Supplementary Table 1. Shortlist of the 311 studies that have been retrieved from the literature search

Search Criteria:
Web of Knowledge (from All Databases)
 TITLE: (prostate) AND TOPIC: (proteom* OR protein) NOT TOPIC: (rat OR mouse OR methylation) AND TOPIC: (urin*)
Refined by: DOCUMENT TYPES: (ARTICLE) AND DOCUMENT TYPES: (ARTICLE)
Timespan: 2006-2015.

Study Authors (Year) Title Journal, Volume (Issue), Page number
Agarwal, M., et al. (2013). "CCL11 (eotaxin-1): A new diagnostic serum marker for prostate cancer." Prostate 73(6): 573-581.

BACKGROUND The recent recommendation of the U.S. Preventive Services Task Force against PSA-based screening for prostate cancer was based, in part, on the lack of demonstrated diagnostic utility of serum PSA values in the low, but detectable range to successfully predict prostate cancer. Though controversial, this recommendation reinforced the critical need to develop, validate, and determine the utility of other serum and/or urine transcript and protein markers as diagnostic markers for PCa. The studies described here were intended to determine whether inflammatory cytokines might augment serum PSA as a diagnostic marker for prostate cancer. METHODS Multiplex ELISA assays were performed to quantify CCL1, CCL2, CCL5, CCL8, CCL11, CCL17, CXCL1, CXCL5, CXCL8, CXCL10, CXCL12, and IL-6 protein levels in the serum of 272 men demonstrating serum PSA values of <10ng/ml and undergoing a 12 core diagnostic needle biopsy for detection of prostate cancer. Logistic regression was used to identify the associations between specific chemokines and prostate cancer status adjusted for prostate volume, and baseline PSA. RESULTS Serum levels for CCL1 (I-309) were significantly elevated among all men with enlarged prostates (P<0.04). Serum levels for CCL11 (Eotaxin-1) were significantly elevated among men with prostate cancer regardless of prostate size (P<0.01). The remaining 10 cytokines examined in this study did not exhibit significant correlations with either prostate volume or cancer status. CONCLUSIONS Serum CCL11 values may provide a useful diagnostic tool to help distinguish between prostatic enlargement and prostate cancer among men demonstrating low, but detectable, serum PSA values. Prostate 73: 573581, 2013. (c) 2012 Wiley Periodicals, Inc.

Ahuja, A., et al. (2011). "Adenoid cystic carcinoma of the prostate: Case report on a rare entity and review of the literature." Pathology Research and Practice 207(6): 391-394.

Adenoid cystic carcinoma is an unusual histological variant of prostatic carcinoma. Because of its rarity, the natural history of this tumor is not known. Here we report this rare entity in a 62-year-old man who presented with symptoms of urinary tract obstruction. Digital rectal examination and ultrasonography (USG) showed an enlarged hard nodular prostate. Serum prostate-specific antigen (PSA) and prostatic acid phosphate levels were found to be within the normal range. Transrectal ultrasound-guided 12 core biopsies of prostate showed morphological features of an adenoid cystic carcinoma in 8 cores (bilateral, mid and base) on histopathological examination. Immunohistochemistry performed for PSA on paraffin section was negative. After diagnosis, bilateral orchidectomy was performed, and hormonal therapy was started in the form of androgen receptor blocker. The patient was clinically stable during a limited follow up of six months. (C) 2011 Elsevier GmbH. All rights reserved.

Al-Azayzih, A., et al. (2012). "TGF beta 1 induces apoptosis in invasive prostate cancer and bladder cancer cells via Akt-independent, p38 MAPK and JNK/SAPK-mediated activation of caspases." Biochemical and Biophysical Research Communications 427(1): 165-170.

Recent findings indicate that advanced stage cancers shun the tumor suppressive actions of TGF beta and inexplicably utilize the cytokine as a tumor promoter. We investigated the effect of TGF beta 1 on the survival and proliferation of invasive prostate (PC3) and bladder (T24) cancer cells. Our study indicated that TGF beta 1 decreased cell viability and induced apoptosis in invasive human PC3 and 124 cells via activation of p38 MAPK-JNK-Caspase9/8/3 pathway. Surprisingly, no change in the phosphorylation of pro-survival Akt kinase was observed. We postulate that TGF beta 1 pathway may be utilized for specifically targeting urological cancers without inflicting side effects on normal tissues. (C) 2012 Elsevier Inc. All rights reserved.

Alecsandru, D., et al. (2006). "E-Coli multiresistant meningitis after transrectal prostate biopsy." Thescientificworldjournal 6: 2323-2326.

Escherichia coli meningitis is a frequent pathology in children younger than 3 years old, but is an uncommon disease in adults. E. coli infection is the main cause of intrahospital bacteremia as a consequence of the employment of different medical procedures. Our patient, male, 69 years old, presented with fever, progressive difficulty in breathing, and shivers 24 h after transrectal prostate biopsy, with an absence of any other symptoms. He received prophylactic treatment with ciprofloxacin and later empirical treatment with ampicillin and tobramicin. After that, the patient presented with fever, headache, behavioral changes, somnolence, disorientation, a fluctuating level of conscience, cutaneous widespread pallor, and acute urinary retention. On physical exploration, we observed generalized hypoventilation, Glasgow 10, stiffness of the neck, inconclusive Kernig; the remaining neurological exploration was normal. Systematic of blood: leukocytes = 8,510/mm(3) (94.5% polymorphonuclear), platelet = 87,000/mm(3), pH = 7.51, pCO(2) = 28.8 mmHg, pO(2) = 61 mmHg, O-2 saturation = 93.8%, and remaining values were normal. Chest X- ray, cranial CT scan, urine cultures were normal. Blood culture: E. coli. CSF: glucose < 0.4 g/l, total proteins = 3.05 g/l, PMN = 7 cells. Microscopic examination of the CSF: Gram-negative bacilli; CSF's culture: abundant E. coli. The case of acute meningitis by multiresistant E. coli after transrectal prostate biopsy presented demonstrates that antibiotic prevention with ciprofloxacin is not absolutely risk free. Besides the use of antibiotic prevention for multiresistant microorganisms, the urologist and other physicians involved in the procedure must not forget that the rate of major complications of transrectal prostate biopsy is 1%, especially when it is performed in patients who will not benefit from that biopsy.

Alsharif, M., et al. (2008). "Cytologic diagnosis of metastatic seminoma to the prostate and urinary bladder: A case report." Diagnostic Cytopathology 36(10): 734-738.

A 42-year-old man presented with severe abdominal pain, constipation, and hematuria. The patient had a history of seminoma treated by chemotherapy followed by bilateral orchiectomy and retroperitoneal lymph node dissection 16 years earlier. A computed tomography (CT) scan showed a 8.0 x 6.0 x 5.0 cm mass in the retrovesical space, encompassing the left side of his proximal bladder, the prostate, and the rectum. A urine cytologic specimen showed loosely cohesive cell clusters composed of highly atypical large cells and occasional large, single cells with macronucleoli present in a background of mainly lymphocytes and histiocytes was diagnosed as recurrent seminoma. Prostate biopsies showed extensively necrotic seminoma with accompanying granulomatous reaction. The tumor cells were immunoreactive for c-kit (CD117), placental-like alkaline phosphatase (PLAP), D2-40, and OCT4. To our knowledge, this is the second report on urine cytology of metastatic seminoma. Diagn, Cytopathol, 2008;36:734-738. (C) 2008 Wiley-Liss, Inc.

Alvarez, F. J., et al. (2007). "3-Phosphoinositide-dependent protein kinase-1/Akt signalling and inhibition in a canine prostate carcinoma cell line." Veterinary and Comparative Oncology 5(1): 47-58.

Deregulation of the 3-phosphoinositide-dependent protein kinase-1 (PDK-1)/Akt signalling pathway is associated with prostate cancer development and progression. Inhibition of PDK-1/Akt signalling can be achieved using structurally optimized celecoxib derivatives such as OSU-03012. In this study, we treated the novel canine prostate cancer cell line, Ace-1, with OSU-03012 or dimethyl sulphoxide in vitro. We found that At was constitutively phosphorylated in the canine prostate cancer cell line Ace-1 and that there was a dose-dependent decrease in cell viability, and At and glycogen synthase kinase-3 beta phosphorylation, in response to OSU-03012 treatment. This was accompanied by a dose-dependent increase in apoptosis. These data suggest that At signalling pathway inhibition is a potential strategy for the treatment of dogs with prostate cancer and that canine prostate cancer is a relevant large animal model for evaluating Akt pathway inhibitors such as OSU-03012 for use in people.

Amini, S., et al. (2014). "The expressions of stem cell markers: Oct4, Nanog, Sox2, nucleostemin, Bmi, Zfx, Tcl1, Tbx3, Dppa4, and Esrrb in bladder, colon, and prostate cancer, and certain cancer cell lines." Anatomy & cell biology 47(1): 1-11.

Uncontrolled self-renewal plays a direct function in the progression of different types of carcinomas. The same molecular pathway that manages self-renewal in normal stem cells also seems to manage cancer stem cells. Here, we examine the expressions of self-renewal regulatory factors Oct4, Nanog, Sox2, nucleostemin, Zfx, Esrrb, Tcl1, Tbx3, and Dppa4 in tissue samples of colon, prostate, and bladder carcinomas as well as cancer cell lines HT-29, Caco-2, HT-1376, LNCaP, and HepG2. We used reverse transcriptase polymerase chain reaction to examine expressions of the above mentioned regulatory factors in cancer cell lines HT-29, Caco-2, HT-1376, LNCaP, and HepG2 and in 20 tumor tissue samples. Total RNA was isolated by the ISOGEN method. RNA integrity was checked by agarose gel electrophoresis and spectrophotometry. Expressions of Oct4 and nucleostemin at the protein level were determined by immunocytochemistry. A significant relationship was found between tumor grade and self-renewal gene expression. Expressions of stem cell specific marker genes were detected in all examined cancer cell lines, in 40% to 100% of bladder cancer samples, and in 60% to 100% of colon and prostate cancer samples. Oct4 expressed in 100% of tumor tissue samples. Our data show that stem cell markers Oct4, Nanog, Sox2, nucleostemin, Bmi, Zfx, Esrrb, Tcl1, Tbx3, and Dppa4 significantly express in cancer cell lines and cancer tissues. Hence, these markers might be useful as potential tumor markers in the diagnosis and/or prognosis of tumors.

Ananthanarayanan, V., et al. (2006). "Alteration of proliferation and apoptotic markers in normal and premalignant tissue associated with prostate cancer." Bmc Cancer 6.

Background: Molecular markers identifying alterations in proliferation and apoptotic pathways could be particularly important in characterizing high-risk normal or pre-neoplastic tissue. We evaluated the following markers: Ki67, Minichromosome Maintenance Protein-2 (Mcm-2), activated caspase-3 (a-casp3) and Bcl-2 to determine if they showed differential expression across progressive degrees of intraepithelial neoplasia and cancer in the prostate. To identify field effects, we also evaluated whether high-risk expression patterns in normal tissue were more common in prostates containing cancer compared to those without cancer (supernormal), and in histologically normal glands adjacent to a cancer focus as opposed to equivalent glands that were more distant. Methods: The aforementioned markers were studied in 13 radical prostatectomy (RP) and 6 cystoprostatectomy (CP) specimens. Tissue compartments representing normal, low grade prostatic intraepithelial neoplasia (LGPIN), high grade prostatic intraepithelial neoplasia (HGPIN), as well as different grades of cancer were mapped on H&E slides and adjacent sections were analyzed using immunohistochemistry. Normal glands within 1 mm distance of a tumor focus and glands beyond 5 mm were considered "near" and "far", respectively. Randomly selected nuclei and 40 x fields were scored by a single observer; basal and luminal epithelial layers were scored separately. Results: Both Ki-67 and Mcm-2 showed an upward trend from normal tissue through HGPIN and cancer with a shift in proliferation from basal to luminal compartment. Activated caspase-3 showed a significant decrease in HGPIN and cancer compartments. Supernormal glands had significantly lower proliferation indices and higher a-casp3 expression compared to normal glands. "Near" normal glands had higher Mcm-2 indices compared to "far" glands; however, they also had higher a-casp3 expression. Bcl-2, which varied minimally in normal tissue, did not show any trend across compartments or evidence for field effects. Conclusion: These results demonstrate that proliferation and apoptosis are altered not only in preneoplastic lesions but also in apparently normal looking epithelium associated with cancer. Luminal cell expression of Mcm-2 appears to be particularly promising as a marker of high-risk normal epithelium. The role of apoptotic markers such as activated caspase-3 is more complex, and might depend on the proliferation status of the tissue in question.

Andriole, G. L., et al. (2010). "Effect of Dutasteride on the Risk of Prostate Cancer." New England Journal of Medicine 362(13): 1192-1202.

Background: We conducted a study to determine whether dutasteride reduces the risk of incident prostate cancer, as detected on biopsy, among men who are at increased risk for the disease. Methods: In this 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, we compared dutasteride, at a dose of 0.5 mg daily, with placebo. Men were eligible for inclusion in the study if they were 50 to 75 years of age, had a prostate-specific antigen (PSA) level of 2.5 to 10.0 ng per milliliter, and had had one negative prostate biopsy (6 to 12 cores) within 6 months before enrollment. Subjects underwent a 10-core transrectal ultrasound-guided biopsy at 2 and 4 years. Results: Among 6729 men who underwent a biopsy or prostate surgery, cancer was detected in 659 of the 3305 men in the dutasteride group, as compared with 858 of the 3424 men in the placebo group, representing a relative risk reduction with dutasteride of 22.8% (95% confidence interval, 15.2 to 29.8) over the 4-year study period (P<0.001). Overall, in years 1 through 4, among the 6706 men who underwent a needle biopsy, there were 220 tumors with a Gleason score of 7 to 10 among 3299 men in the dutasteride group and 233 among 3407 men in the placebo group (P=0.81). During years 3 and 4, there were 12 tumors with a Gleason score of 8 to 10 in the dutasteride group, as compared with only 1 in the placebo group (P=0.003). Dutasteride therapy, as compared with placebo, resulted in a reduction in the rate of acute urinary retention (1.6% vs. 6.7%, a 77.3% relative reduction). The incidence of adverse events was similar to that in studies of dutasteride therapy for benign prostatic hyperplasia, except that in our study, as compared with previous studies, the relative incidence of the composite category of cardiac failure was higher in the dutasteride group than in the placebo group (0.7% [30 men] vs. 0.4% [16 men], P=0.03). Conclusions: Over the course of the 4-year study period, dutasteride reduced the risk of incident prostate cancer detected on biopsy and improved the outcomes related to benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00056407.) N Engl J Med 2010;362:1192-202.

Annels, N. E., et al. (2014). "Spontaneous antibodies against Engrailed-2 (EN2) protein in patients with prostate cancer." Clinical and Experimental Immunology 177(2): 428-438.

We reported the expression of the homeodomain-containing transcription factor Engrailed-2 (EN2) in prostate cancer and showed that the presence of EN2 protein in the urine was highly predictive of prostate cancer. This study aimed to determine whether patients with prostate cancer have EN2 autoantibodies, what the prevalence of these antibodies is and whether they are associated with disease stage. The spontaneous immunoglobulin (Ig)G immune response against EN2 and for comparison the tumour antigen New York Esophageal Squamous Cell Carcinoma 1 (NY-ESO-1), were tested by enzyme-linked immunosorbent assay (ELISA) in three different cohorts of prostate cancer patients as well as a group of men genetically predisposed to prostate cancer. Thirty-two of 353 (9.1%) of the SUN cohort representing all stages of prostate cancer demonstrated EN2 IgG responses, 12 of 107 patients (11.2%) in the advanced prostate cancer patients showed responses, while only four of 121 patients (3.3%) with castrate-resistant prostate cancer showed EN2 autoantibodies. No significant responses were found in the predisposed group. Anti-EN2 IgG responses were significantly higher in patients with prostate cancer compared to healthy control males and similarly prevalent to anti-NY-ESO-1 responses. While EN2 autoantibodies are not a useful diagnostic or monitoring tool, EN2 immunogenicity provides the rationale to pursue studies using EN2 as an immunotherapeutic target.

Arlen, P. M., et al. (2007). "Clinical safety of a viral vector based prostate cancer vaccine strategy." Journal of Urology 178(4): 1515-1520.

Purpose: The primary objective of this phase I study was to evaluate the clinical safety of a vaccine using recombinant vaccinia virus (prime) and recombinant fowlpox virus (boost) in combination with granulocyte-macrophage colony-stimulating factor in patients with prostate cancer. The vaccines contained transgenes for prostate specific antigen, a triad of co-stimulatory molecules and a tumor antigen whose amino acid sequence had been modified to enhance its immunogenicity. Secondary end points were immunological and clinical responses, changes in prostate specific antigen velocity, and the kinetics of vaccinia virus clearance from the vaccination site, serum, peripheral blood mononuclear cells, urine and saliva. Materials and Methods: The 15 patients enrolled in this study had metastatic prostate cancer. Patients were given recombinant fowlpox-prostate specific antigen/triad of co-stimulatory molecules alone or recombinant vaccinia-prostate specific antigen/triad of co-stimulatory molecules followed by recombinant fowlpox-prostate specific antigen/triad of costimulatory molecules on a prime and boost schedule with or without recombinant-granulocyte-macrophage colony-stimulating factor protein or recombinant fowlpox-granulocyte-macrophage colony-stimulating factor vector. Prostate specific antigen specific immune responses were measured using an enzyme-linked immunosorbent spot assay for interferon-gamma production. Polymerase chain reaction for vaccinia DNA and a plaque assay for live virus were also used. Results: Some grade 2 toxicity was seen in patients who received a higher dose of recombinant fowlpox-granulocytemacrophage colony-stimulating factor but no toxicity exceeded grade 2. Viable vaccinia was detected after vaccination at the site swab of 1 of 4 patients analyzed. Prostate specific antigen specific immune responses were seen in 4 of 6 patients who were HLA-A2+ and decreases in serum prostate specific antigen velocity were observed in 9 of 15. Conclusions: Based on the safety and preliminary immunogenicity results of this trial we recommend initiating a randomized, phase II study of prostate specific antigen/triad of co-stimulatory molecules vaccines in patients with less advanced prostate cancer.

Attard, G., et al. (2012). "Clinical and Biochemical Consequences of CYP17A1 Inhibition with Abiraterone Given with and without Exogenous Glucocorticoids in Castrate Men with Advanced Prostate Cancer." Journal of Clinical Endocrinology & Metabolism 97(2): 507-516.

Context: Abiraterone acetate is a small-molecule cytochrome P450 17A1 (CYP17A1) inhibitor that is active in castration-resistant prostate cancer. Objective: Our objective was to determine the impact of abiraterone with and without dexamethasone treatment on in vivo steroidogenesis. Design and Methods: We treated 42 castrate, castration-resistant prostate cancer patients with continuous, daily abiraterone acetate and prospectively collected blood and urine before and during abiraterone treatment and after addition of dexamethasone 0.5 mg daily. Results: Treatment with single-agent abiraterone acetate was associated with accumulation of steroids with mineralocorticoid properties upstream of CYP17A1. This resulted in side effects, including hypertension, hypokalemia, and fluid overload, in 38 of 42 patients that were generally treated effectively with eplerenone. Importantly, serum and urinary androgens were suppressed by more than 90% from baseline. Urinary metabolites of 17-hydroxypregnenolone and 17-hydroxyprogesterone downstream of 17 alpha-hydroxylase remained unchanged. However, 3 alpha 5 alpha-17-hydroxypregnanolone, which can be converted via the backdoor pathway toward 5 alpha-dihydrotestosterone, increased significantly and correlated with levels of the major 5 alpha-dihydrotestosterone metabolite androsterone. In contrast, urinary metabolites of 11-deoxycortisol and active glucocorticoids declined significantly. Addition of dexamethasone to abiraterone acetate significantly suppressed ACTH and endogenous steroids, including 3 alpha 5 alpha-17-hydroxypregnanolone. Conclusion: CYP17A1 inhibition with abiraterone acetate is characterized by significant suppression of androgenandcortisol synthesis. The latter is associated with a rise in ACTH that causes raised mineralocorticoids, leading to side effects and incomplete 17 alpha-hydroxylase inhibition. Concomitant inhibition of 17,20-lyase results in diversion of 17-hydroxyprogesterone metabolites toward androgen synthesis via the backdoor pathway. Addition of dexamethasone reverses toxicity and could further suppress androgens by preventing a rise in substrates of backdoor androgen synthesis. (J Clin Endocrinol Metab 97:507-516, 2012)

Azumi, M., et al. (2010). "Six-Transmembrane Epithelial Antigen of the Prostate as an Immunotherapeutic Target for Renal Cell and Bladder Cancer." Journal of Urology 183(5): 2036-2044.

Purpose: T-cell based immunotherapy for renal cell and bladder cancer is one of the most promising therapeutic approaches. STEAP is a novel cell surface protein that is over expressed in various cancers, including renal cell and bladder cancer. Recently we induced STEAP specific helper T lymphocytes that recognize the naturally processed STEAP peptide epitopes STEAP(102-116) and STEAP(192-206) arising from STEAP expressing tumor cells. Thus, STEAP may be a useful tumor associated antigen for designing T-cell based immunotherapy. We determined whether STEAP could induce anti-cellular immune responses to urological cancer. Materials and Methods: We selected 2 previously described STEAP derived epitope peptides, STEAP(102-116) and STEAP(192-206), and examined their ability to elicit helper T-lymphocyte responses by in vitro vaccination of CD4 T lymphocytes from healthy individuals and patients with cancer. Results: STEAP peptides induced helper T-lymphocyte responses using lymphocytes from healthy individuals that directly recognized STEAP expressing, DR positive renal cell and bladder cancer cells, and autologous dendritic cells pulsed with STEAP expressing tumor cell lysates in a major histocompatibility complex class II restricted manner. These peptides also stimulated T-cell responses in patients with renal cell or bladder cancer. Each STEAP peptides behaved as a promiscuous T-cell epitope, in that they stimulated T cells in the context of multiple major histocompatibility complex class II alleles. Conclusions: Results show that STEAP helper T-lymphocyte epitopes could be used to optimize T-cell based immunotherapy against STEAP expressing renal cell and bladder cancer.

Bai, V. U., et al. (2010). "Androgen regulated TRPM8 expression: A potential mRNA marker for metastatic prostate cancer detection in body fluids." International Journal of Oncology 36(2): 443-450.

Identification of sensitive and specific biomarkers for early detection and prognosis of prostate cancer is essential for timely and appropriate treatment of the disease in individual patients. We identified an RNA transcript with sequence homology to TRPM8 (melastatin-related transient receptor potential member 8) that was overexpressed in tumor vs. patient-matched non-tumor prostate tissues by RT-PCR differential display (DD). Semi-quantitative RT-PCR analysis revealed that TRPM8 levels were higher in tumor than in non-tumor tissue from 31 of 40 (>75%) patients examined. Overexpression of TRPM8 was independent of changes in androgen receptor (AR) mRNA levels in tumor tissue. However, in studies with established cell lines, TRPM8 expression was detectable only in AR-positive, but not in AR-negative cells, and it was suppressed by steroid deprivation or anti-androgen bicalutamide (Casodex) treatment, suggesting the requirement of AR activity for TRPM8 expression in prostate cancer cells. TRPM8 mRNA was also detected in body fluids of men. Most importantly, its levels were significantly higher (p<0.001, n=18) in urine and blood of patients with metastatic disease than in those of healthy men. However, there was no significant difference (p>0.05, n=10) in its levels between prostate cancer patients with localized disease and healthy men. Together, these studies demonstrate that TRPM8 expression is androgen regulated in prostate cancer cells and that, while tissue TRPM8 mRNA levels can be used for detection of prostate cancer, urine and blood TRPM8 mRNA levels may prove to be useful for distinguishing metastatic disease from clinically localized prostate cancer at the time of diagnosis.

Bardan, R., et al. (2014). "The role of prostatic inflammation biomarkers in the diagnosis of prostate diseases." Clinical Biochemistry 47(10-11): 909-915.

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are chronic conditions, which are hormone-dependent and epidemiologically associated with prostate inflammation. As a large number of studies have demonstrated, the stimulation of T-cells at the level of prostatic chronic inflammatory infiltrates is followed by stromal and epithelial cell proliferation. The aim of this review is to present the actual level of knowledge in the field of prostatic immune response and chronic inflammation, and to analyze the relationships between chronic inflammation and BPH/PCa. The most studied prostatic inflammation biomarkers detected in biological fluids are also presented, together with their potential roles in the diagnosis and prognosis of prostatic disease. (C) 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Barry, M., et al. (2007). "TMPRSS2-ERG fusion heterogeneity in Multifocal prostate cancer: Clinical and biologic implications." Urology 70(4): 630-633.

OBJECTIVES To characterize the clonality of TMPRSS2-ERG fusion in multifocal prostate cancer. METHODS From 80 consecutive radical prostatectomy specimens, we identified 32 cases with multiple spatially separate tumors. In each case, we assessed two to three tumor foci for TMPRSS2-ERG fusion using an ERG break-apart interphase fluorescence in situ hybridization assay. RESULTS Individual tumor foci showed homogenity for fusion status (intrafocal clonal homogenity). In 19 (59%) of the 32 cases, all foci within a case had the same fusion status (interfocal homogeneity). In 15 (80%) of the 19 cases, no foci had fusion, and in 4 (20%), all foci had fusion. Of the 32 cased, 13 (41%) demonstrated heterogeneity for fusion status within a case (interfocal clonal heterogeneity). CONCLUSIONS In this study, we have demonstrated interfocal heterogeneity and intrafocal homogeneity for TMPRSS2-ERG fusion in prostate cancer with multiple tumors. These findings support the multiclonal nature of prostate cancer with clinical implications for needle biopsy strategies and the development of urine-based screening tests.

Bauer, R. M., et al. (2011). "Coupling of alpha(1)-Adrenoceptors to ERK1/2 in the Human Prostate." Urologia Internationalis 86(4): 427-433.

Introduction: alpha(1)-Adrenoceptors are considered critical for the regulation of prostatic smooth muscle tone. However, previous studies suggested further alpha(1)-adrenoceptor functions besides contraction. Here, we investigated whether alpha(1)-adrenoceptors in the human prostate may activate extracellular signal-regulated kinases (ERK1/2). Methods: Prostate tissues from patients undergoing radical prostatectomy were stimulated in vitro. Activation of ERK1/2 was assessed by Western blot analysis. Expression of ERK1/2 was studied by immunohistochemistry. The effect of ERK1/2 inhibition by U0126 on phenylephrine-induced contraction was studied in organ-bath experiments. Results: Stimulation of human prostate tissue with noradrenaline (30 mu M) or phenylephrine (10 mu M) resulted in ERK activation. This was reflected by increased levels of phosphorylated ERK1/2. Expression of ERK1/2 in the prostate was observed in smooth muscle cells. Incubation of prostate tissue with U0126 (30 mu M) resulted in ERK1/2 inhibition. Dose-dependent phenylephrine-induced contraction of prostate tissue was not modulated by U0126. Conclusions: alpha(1)-Adrenoceptors in the human prostate are coupled to ERK1/2. This may partially explain previous observations suggesting a role of alpha(1)-adrenoceptors in the regulation of prostate growth. Copyright (C) 2011 S. Karger AG, Basel

Baydar, D. E. and F. T. Aki (2011). "Low-grade fibromyxoid sarcoma metastatic to the prostate." Annals of Diagnostic Pathology 15(1): 64-68.

Spindle cell tumors of the prostate are rare and mostly primary. We report a case of retroperitoneal sarcoma, which is a low-grade fibromyxoid sarcoma involving the prostate secondarily by metastasis. The patient was a 44-year-old man who presented with progressing abdominal pain. Computed tomography showed a large retroperitoneal mass. The patient underwent surgical resection. Intraoperatively, a second smaller mass was identified in the pelvis and was left untouched. The resected retroperitoneal specimen and prostate transrectal needle biopsies taken afterward showed the same mesenchymal tumor. Radical cystoprostatectomy was performed. Metatatic tumor involving the prostate, bilateral seminal vesicles, and base of the urinary bladder was found. Microscopic examination revealed typical histomorphologic features of low-grade fibromyxoid sarcoma. The patient is without evidence of disease 3 years postoperatively. This case is the first documentation of metastatic sarcoma to the prostate and expands the list of malignant mesenchymal neoplasms that may involve this organ. (C) 2011 Elsevier Inc. All rights reserved.

Berges, R., et al. (2011). "Association of polymorphisms in CYP19A1 and CYP3A4 genes with lower urinary tract symptoms, prostate volume, uroflow and PSA in a population-based sample." World Journal of Urology 29(2): 143-148.

The known importance of testosterone for the development of benign prostatic hyperplasia (BPH) prompted us to test the hypothesis whether polymorphisms of two genes (CYP19A1 and CYP3A4) involved in testosterone metabolism are associated with clinical BPH-parameters. A random sample of the population-based Herne lower urinary tract symptoms cohort was analysed. All these men underwent a detailed urological work-up. Two polymorphisms in the CYP19A1 gene [rs700518 in exon 4 (A57G); rs10046 at the 3'UTR(C268T)] and one in the 3'UTR of CYP3A4 [rs2740574 (A392G)] were determined by TaqMan assay from genomic DNA of peripheral blood. These polymorphisms were correlated to clinical and laboratory BPH-parameters. A total of 392 men (65.4 +/- A 7.0 years; 52-79 years) were analysed. Mean International Prostate Symptom Score (IPSS; 7.5), Q (max) (15.4 ml/s), prostate volume (31 ml) and prostate specific antigen (PSA) (1.8 ng/ml) indicated a typical elderly population. Both polymorphisms in the CYP19A1 gene were not correlated to age, IPSS, Q (max), prostate volume and post-void residual volume. Serum PSA was higher in men carrying the heterozygous rs10046 genotype (2.0 +/- A 0.1 ng/ml) than in those with the CC-genotype (1.7 +/- A 0.2 ng/ml, P = 0.012). Men carrying one a mutated allele of the CYP3A4 gene had smaller prostates (27.0 +/- A 2.0 vs. 32 +/- A 0.8 ml, P = 0.02) and lower PSA levels (1.6 +/- A 0.3 vs. 1.9 +/- A 0.1 ng/ml). The inconsistent associations observed herein and for other gene polymorphisms warrant further studies. In general, the data regarding the association of gene polymorphism to BPH-parameters suggest that this disease is caused by multiple rather than a single genetic variant. A rigorous patient selection based on anatomo-pathological and hormonal profile may possible reduce the number of confounders for future studies thus enabling a more detailed assessment of the association between genetic factors and BPH-parameters.

Bezerra, S. M., et al. (2014). "GATA3 expression in small cell carcinoma of bladder and prostate and its potential role in determining primary tumor origin." Human Pathology 45(8): 1682-1687.

GATA3 is a sensitive marker for urothelial carcinoma. We here evaluate, for the first time, GATA3 expression in small cell carcinoma of bladder and prostate and assess its utility in the differential diagnosis with small cell carcinoma of lung primary. Archival tissues from 60 small cell carcinomas (12 bladder, 15 lung, and 33 prostate primary cases) were used to build 2 tissue microarrays. We also assessed whole slide sections from 10 additional primary small cell carcinomas of bladder. GATA3 nuclear expression was evaluated using standard immunohistochemistry. Intensity (weak, moderate, and strong) and extent of expression were assessed in each tissue microarray spot. Extent positivity was categorized as focal (1%-25%), multifocal (>25%), and diffuse (>75%). Nuclear GATA3 expression was encountered in 7 bladder (7/22, 32%) and 2 lung (2/15, 13%) small cell carcinomas. All 33 primary prostate small cell carcinomas were negative. Among bladder tumors, strong and diffuse (>75%) GATA3 labeling was seen in 3 cases (3/22, 14%); focal positivity was observed in the 4 remaining cases (4/22, 18%). Both positive lung cases had only focal positivity. Our study is the first to reveal GATA3 expression in the small subset of lung small cell carcinoma that should be taken into consideration in assigning site of origin in advanced small cell carcinoma cases. Our novel finding of GATA3 positivity in one-third of bladder small cell carcinoma is of potential value in differentiating small cell carcinomas of prostate origin from those of bladder origin. (C) 2014 Elsevier Inc. All rights reserved.

Bickers, B. and C. Aukim-Hastie (2009). "New Molecular Biomarkers for the Prognosis and Management of Prostate Cancer - The Post PSA Era." Anticancer Research 29(8): 3289-3298.

The widespread use of the PSA test has led to increased detection of the disease at earlier stages and a reduction in the number of patients where metastatic disease is found at diagnosis. However, there are significant limitations to the PSA test such as its lack of specificity, elevation in benign disease and failure to detect a significant number of PSA-negative tumours. Therefore, PSA is now commonly regarded as an indicator of prostate volume and is not independently diagnostic or prognostic in prostate cancer. Due to these limitations, there is an urgent need for new prognostic biomarkers to enhance the clinical management of prostate cancer. There have been many recent advances in high-throughput technologies for measuring gene and protein expression in minimally invasive samples (e.g. blood, urine) that could more accurately predict disease progression. This review article gives a brief overview of biomarkers that are currently showing prognostic potential in prostate cancer research.

Bijnsdorp, I. V., et al. (2013). "Exosomal ITGA3 interferes with non-cancerous prostate cell functions and is increased in urine exosomes of metastatic prostate cancer patients." Journal of extracellular vesicles 2.

BACKGROUND: Cancer cells are able to change the protein expression and behavior of non-cancerous surrounding cells. Exosomes, secreted by prostate cancer (PCa) cells, may have a functional role in cancer metastasis and present a promising source for protein biomarkers. The aim of the present study was to identify which proteins in exosomes can influence non-cancerous cells, and to determine whether we can use urine exosomal proteins to identify high-risk PCa patients. METHOD: Exosomes were isolated by ultracentrifugation. Migration and invasion were studied by the transwell (invasion) assay. Proteomics was performed by LC-MS/MS and identified proteins were validated by Western blotting. Cellular uptake of fluorescent labeled PKH67-exosomes was measured by FACS. RESULTS: Based on comparative protein profiling by mass spectrometry-based proteomics of LNCaP- and PC3-exosomes, we selected ITGA3 and ITGB1, involved in migration/invasion, for further analyses. Inhibition of exosomal ITGA3 reduced the migration and invasion of non-cancerous prostate epithelial cells (prEC) almost completely. Cellular uptake of exosomes by prEC was higher with PC3-exosomes compared to LNCaP exosomes. Finally, ITGA3 and ITGB1 were more abundant in urine exosomes of metastatic patients (p<0.05), compared to benign prostate hyperplasia or PCa. CONCLUSION: These data indicate exosomal ITGA3 and ITGB1 may play a role in manipulating non-cancerous surrounding cells and that measurement of ITGA3 and ITGB1 in urine exosomes has the potential to identify patients with metastatic PCa in a non-invasive manner.

Bilgin Dogru, E., et al. (2014). "EMMPRIN and ADAM12 in prostate cancer: preliminary results of a prospective study." Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine 35(11): 11647-11653.

Extracellular metalloproteinase inducer (EMMPRIN) and a disintegrin and metalloproteinase (ADAM12) play a major role in cancer invasion and metastasis owing to the fact that they are directly related to the cell microenvironment and extracellular matrix (ECM) degradation. The aim of this study was to search for an answer to the question "whether the determination of EMMPRIN and ADAM12 values especially in urine may be helpful for the early diagnosis of prostate cancer without employing invasive methods" and also to check whether they may be useful for the determination of the patients with high metastasis risk. Peripheral blood and urine from 66 prostate cancer patients (40 local, 20 locally advanced, 6 metastatic) and 14 healthy controls were evaluated by enzyme-linked immunosorbent assay (ELISA) method. Serum EMMPRIN and ADAM12 values of the patients were seen to be statistically higher than the serum EMMPRIN and ADAM12 values of the healthy controls (p=0.01 and p=0.001, respectively). The urine ADAM12 levels were significantly higher in patients (p=0.013). No significant relationships were found between urine EMMPRIN values of the patients and the healthy controls (p>0.05). Positive correlation between urine EMMPRIN-urine ADAM12 tests was found in total patients group (r=0.683, p=0.001). Our preliminary results revealed that serum EMMPRIN and ADAM12 values and urine ADAM12 values may be useful markers in prostate cancer therapy. Due to the high correlation between these two tests, we are of the opinion that the use of urine ADAM12 in clinic may be sufficient and favorable together with prostate-specific antigen (PSA) for treatment.

Bonetti, L. R., et al. (2011). "An unusual case of signet ring cell adenocarcinoma of the prostate." Pathologica 103(2): 40-42.

We report the case of a 70-year-old man with symptoms of urinary obstruction and haematuria, with histological diagnosis of primary signet-ring cell carcinoma of the prostate. Almost 90% of the tumour cells contained characteristic intracytoplasmic vacuoles that positively stained with diastase-digested PAS, Alcian blue and mucicarmine. The positive immunostaining for PSA and PSAP confirmed the prostatic origin of the tumour. Although the patient received hormonal therapy, the disease progressed and the patient died 11 months after surgery.

Bu, H., et al. (2011). "The Anterior Gradient 2 (AGR2) Gene Is Overexpressed in Prostate Cancer and May Be Useful as a Urine Sediment Marker for Prostate Cancer Detection." Prostate 71(6): 575-587.

BACKGROUND. AGR2 is a member of the endoplasmatic reticulum protein disulphide isomerase gene family implicated in tumor metastasis. Its expression pattern, function, and utility as a marker remains to be further investigated. METHODS. Using real-time RT-PCR and immunohistochemistry, changes of expression in different tumor stages were explored in microdissected tumor samples. AGR2 transcript level in urine sediments was scrutinized for suitability as a tumor marker. AGR2 androgen regulation and function were analyzed in cellular prostate cancer models. RESULTS. AGR2 is highly expressed in prostate cancer compared to benign tissue in particular also in low-grade tumors and PIN lesions. AGR2 transcripts were detected in urine sediments of patients undergoing prostate biopsy with significantly higher levels in tumor patients. The urine AGR2/PSA transcript ratio allowed much better discrimination between cancer and benign patients than serum total PSA or % free PSA. Prostate tumor cells express and secrete variable amounts of AGR2 protein, the highest level was found in PC3 cells. In androgen receptor-positive cell lines AGR2 is upregulated by androgens. Increased expression enhanced the migratory and invasive potential but decreased growth and proliferation in vitro and in vivo. CONCLUSION. AGR2 enhances the invasion phenotype of prostate cancer cells while at the same time attenuating cell-cycle progression. This function, its expression pattern and the increased level of AGR transcripts in urine sediments of prostate cancer patients call for further exploration as a prostate cancer marker and a modulator of tumor growth and invasion. Prostate 71: 575-587, 2011. (C) 2010 Wiley-Liss, Inc.

Burri, R. J., et al. (2008). "Association of single nucleotide polymorphisms in SOD2, XRCC1 and XRCC3 with susceptibility for the development of adverse effects resulting from radiotherapy for prostate cancer." Radiation Research 170(1): 49-59.

The objective of this study was to determine whether an association exists between certain single nucleotide polymorphisms (SNPs), which have previously been linked with adverse normal tissue effects resulting from radiotherapy, and the development of radiation injury resulting from radiotherapy for prostate cancer. A total of 135 consecutive patients with clinically localized prostate cancer and a minimum of 1 year of follow-up who had been treated with radiation therapy, either brachytherapy alone or in combination with external-beam radiotherapy, with or without hormone therapy, were genotyped for SNPs in SOD2, XRCC1 and XRCC3. Three common late tissue toxicities were investigated: late rectal bleeding, urinary morbidity, and erectile dysfunction. Patients with the XRCC1 rs25489 G/A (Arg280His) genotype were more likely to develop erectile dysfunction after irradiation than patients who had the G/G genotype (67% compared to 24%; P = 0.048). In addition, patients who had the SOD2 rs4880 T/C (Val16Ala) genotype exhibited a significant increase in grade 2 late rectal bleeding compared to patients who had either the CIC or T/T genotype for this SNP (8% compared to 0%; P = 0.02). Finally, patients with the combination of the SOD2 rs4880 C/T genotype and XRCC3 rs861539 T/C (Thr241Met) genotype experienced a significant increase in grade 2 late rectal bleeding compared to patients without this particular genotypic arrangement (14% compared to 1%; P = 0.002). These results suggest that SNPs in the SOD2, XRCC1 and XRCC3 genes are associated with the development of late radiation injury in patients treated with radiation therapy for prostate adenocarcinoma. (C) 2008 by Radiation Research Society.

Calmasini, F. B., et al. (2015). "The Beta-3 Adrenoceptor Agonist, Mirabegron Relaxes Isolated Prostate From Human and Rabbit: New Therapeutic Indication?" Prostate 75(4): 440-447.

BACKGROUNDAlpha1 (1)-blockers, 5-alpha reductase and phosphodiesterase type-5 inhibitors are pharmacological classes currently available for benign prostatic hyperplasia (BPH) treatment. Mirabegron, a beta-3 adrenoceptor (3-AR) agonist has been approved for the therapy of overactive bladder and may constitute a new therapeutic option for BPH treatment. This study is aimed to evaluate the in vitro effects of mirabegron in human and rabbit prostatic smooth muscle. METHODSIn rabbit prostate, electrical field stimulation (EFS)-induced contraction and concentration-response curve (CRC) to mirabegron in phenylephrine pre-contracted tissues were carried out. The potency (pEC(50)) and maximal response (E-max) values were determined. In human prostate, CRC to phenylephrine was carried out in the absence and presence of mirabegron. Immunohistochemistry analysis for 3-AR was also carried out. RESULTSIn human prostate, immunohistochemistry analysis revealed the presence of 3-AR on the transition zone and mirabegron reduced by 42% the phenylephrine-induced contractions. In rabbit prostate, mirabegron produced concentration-dependent relaxations (pEC(50): 6.010.12; E-max: 106 +/- 3%), which were fully resistant to the blockade of 1-AR and 2-AR. The 3-AR blocker L748,337 caused a six-fold rightward shift in mirabegron-induced relaxations. Mirabegron (10M) reduced by 63% the EFS-induced contractions. Inhibitors of nitric oxide (L-NAME) and of soluble guanylate cyclase (ODQ) along with a cocktail of K+ channel blockers (apamin, charybdotoxin, glibenclamide, tetraethylammonium) all failed to significantly affect the mirabegron-induced rabbit relaxations. CONCLUSIONMirabegron relaxes prostatic smooth muscle, providing an experimental support for the clinical investigation of its combination with an 1-blockers or PDE5 inhibitors in the treatment of BPH. Prostate 75:440-447, 2015. (c) 2014 Wiley Periodicals, Inc.

Cao, D.-L., et al. (2011). "A Multiplex Model of Combining Gene-Based, Protein-Based, and Metabolite-Based With Positive and Negative Markers in Urine for the Early Diagnosis of Prostate Cancer." Prostate 71(7): 700-710.

BACKGROUND. Multiplex urine-based assay emerged outperforms single biomarker (e. g., prostate-specific antigen, PSA) for predicting prostate cancer (CaP), whereas its combined mode has to be fully optimized. Our aim is to determine whether a strategy of combining gene-based, protein-based, metabolite-based with positive, negative makers in urine could optimize a multiplex model for detecting CaP. METHODS. Using quantitative PCR, Western blot, and liquid chromatography-mass spectrometry, expression patterns of PCA3, TMPRSS2: ERG, Annexin A3, Sarcosine, and urine PSA were evaluated in urine samples from 86 untreated patients with CaP and 45 patients with no evidence of malignancy. Multivariate logistic regression analysis was used to generate a final model and receiver-operating characteristic (ROC) analysis and special bootstrap software to assess diagnostic performance of tested variables. RESULTS. The expression patterns of PCA3, TMPRSS2: ERG, Annexin A3, Sarcosine, and a panel including these biomarkers were significant predictors of CaP both in patients with PSA 4-10 ng/ml and in all patients (all $P < 0.05$). Employing ROC analysis, the area under the curves of the panel in these both cohorts were 0.840 and 0.856, respectively, which outperform that of any single biomarker (PCA3: 0.733 and 0.739; TMPRSS2: ERG: 0.720 and 0.732; Annexin A3: 0.716 and 0.728; Sarcosine: 0.659 and 0.665, respectively). CONCLUSIONS. Compared with single biomarker, the multiplex model including PCA3, TMPRSS2: ERG, Annexin A3 and Sarcosine adds even more to the diagnostic performance for predicting CaP. Further validation experiments and optimization for the strategy of constructing this model are warranted. Prostate 71: 700-710, 2011. (C) 2010 Wiley-Liss, Inc.

Casanova-Salas, I., et al. (2015). "MiR-187 Targets the Androgen-Regulated Gene ALDH1A3 in Prostate Cancer." PloS one 10(5): e0125576-e0125576.

miRNAs are predicted to control the activity of approximately 60% of all protein-coding genes participating in the regulation of several cellular processes and diseases, including cancer. Recently, we have demonstrated that miR-187 is significantly downregulated in prostate cancer (PCa) and here we propose a proteomic approach to identify its potential targets. For this purpose, PC-3 cells were transiently transfected with miR-187 precursor and miRNA mimic negative control. Proteins were analyzed by a two-dimensional difference gel electrophoresis (2D-DIGE) and defined as differentially regulated if the observed fold change was ±1.06. Then, MALDI-TOF MS analysis was performed after protein digestion and low abundance proteins were identified by LC-MS/MS. Peptides were identified by searching against the Expasy SWISS PROT database, and target validation was performed both in vitro by western blot and qRT-PCR and in clinical samples by qRT-PCR, immunohistochemistry and ELISA. DIGE analysis showed 9 differentially expressed spots (p<0.05) and 7 showed a down-regulated expression upon miR-187 re-introduction. Among these targets we identified aldehyde dehydrogenase 1A3 (ALDH1A3). ALDH1A3 expression was significantly downregulated in PC3, LNCaP and DU-145 cells after miR-187 re-introduction. Supporting these data, the expression of ALDH1A3 was found significantly (p<0.0001) up-regulated in PCa samples and inversely correlated (p<0.0001) with miR-187 expression, its expression being directly associated with Gleason score (p = 0.05). The expression of ALDH1A3 was measured in urine samples to evaluate the predictive capability of this biomarker for the presence of PCa and, at a signification level of 10%, PSA and also ALDH1A3 were significantly associated with a positive biopsy of PCa. In conclusion, our data illustrate for the first time the role of ALDH1A3 as a miR-187 target in PCa and provide insights in the utility of using this protein as a new biomarker for PCa.

Cazares, L. H., et al. (2010). "Molecular pathology of prostate cancer." Cancer biomarkers : section A of Disease markers 9(1-6): 441-459.

This chapter includes discussion of the molecular pathology of tissue, blood, urine, and expressed prostatic secretions. Because we are unable to reliably image the disease in vivo, a 12 core method that oversamples the peripheral zone is widely used. This generates large numbers of cores that need to be carefully processed and sampled. In spite of the large number of tissue cores, the amount of tumor available for study is often quite limited. This is a particular challenge for research, as new biomarker assays will need to preserve tissue architecture intact for histopathology. Methods of processing and reporting pathology are discussed. With the exception of ductal variants, recognized subtypes of prostate cancer are largely confined to research applications, and most prostate cancers are acinar. Biomarker discovery in urine and expressed prostatic secretions would be useful since these are readily obtained and are proximate fluids. The well-known challenges of biomarker discovery in blood and urine are referenced and discussed. Mediators of carcinogenesis can serve as biomarkers as exemplified by mutations in PTEN and TMPRSS2:ERG fusion. The use of proteomics in biomarker discovery with an emphasis on imaging mass spectroscopy of tissues is discussed. Small RNAs are of great interest, however, their usefulness as biomarkers in clinical decision making remains the subject of ongoing research. The chapter concludes with an overview of blood biomarkers such as circulating nucleic acids and tumor cells and bound/free isoforms of prostate specific antigen (PSA).

Cazares, L. H., et al. (2011). "Molecular pathology of prostate cancer." Cancer Biomarkers 9(1-6): 441-459.

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Cernei, N., et al. (2013). "Sarcosine as a Potential Prostate Cancer Biomarker-A Review." International Journal of Molecular Sciences 14(7): 13893-13908.

Prostate cancer (CaP) is the most common type of tumour disease in men. Early diagnosis of cancer of the prostate is very important, because the sooner the cancer is detected, the better it is treated. According to that fact, there is great interest in the finding of new markers including amino acids, proteins or nucleic acids. Prostate specific antigen (PSA) is commonly used and is the most important biomarker of CaP. This marker can only be detected in blood and its sensitivity is approximately 80%. Moreover, early stages cannot be diagnosed using this protein. Currently, there does not exist a test for diagnosis of early stages of prostate cancer. This fact motivates us to find markers sensitive to the early stages of CaP, which are easily detected in body fluids including urine. A potential is therefore attributed to the non-protein amino acid sarcosine, which is generated by glycine-N-methyltransferase in its biochemical cycle. In this review, we summarize analytical methods for quantification of sarcosine as a CaP marker. Moreover, pathways of the connection of synthesis of sarcosine and CaP development are discussed.

Cernei, N., et al. (2012). "Spectrometric and Electrochemical Analysis of Sarcosine as a Potential Prostate Carcinoma Marker." International Journal of Electrochemical Science 7(5): 4286-4301.

Sarcosine, also known as N-methylglycine, is a natural ubiquitous non/protein amino acid which occurs as intermediate and side product in glycine synthesis and degradation. Recently, sarcosine has been investigated as a new putative marker in relation to prostate cancer. Sarcosine was identified as a differential metabolite that was greatly increased during prostate cancer progression to metastasis and could be detected in urine. It was also shown, that sarcosine addition to benign prostate cell cultures caused increase of their invasivity and motility. The aim of our study was to propose a low-cost, robust and simple method suitable for sarcosine determination in biological samples such as urine or blood plasma. For this purpose an ion exchange liquid chromatography as robust separation method was tested however this method suffers from insufficient limit of detection at the level of 70 mu M of sarcosine. For more sensitive detection we optimized the off-line approach to ninhydrin derivatization of collected fractions. The fractions were collected and after addition of ninhydrin incubation of the mixture under the optimised temperature and time were done. Analysis of mixture was carried out by the simple UV-VIS spectrometer. The obtained limit of detection for this optimised procedure was promising 1.7 mu M of sarcosine but this value is similar to physiologically occurring concentration of sarcosine in prostate cancer patients. Therefore we optimized the electrochemical method based on analysis of collected fractions by coulometric detection integrated as FIA-ED. Here we obtained the limits of detection of 110 nM of sarcosine, which is more than satisfactory for its determination in various matrixes such as urine or plasma of cancer patients.

Chaffer, C. L., et al. (2006). "PPAR gamma-independent induction of growth arrest and apoptosis in prostate and bladder carcinoma." Bmc Cancer 6.

Background: Although PPAR. antagonists have shown considerable pre-clinical efficacy, recent studies suggest PPAR gamma ligands induce PPAR gamma-independent effects. There is a need to better define such effects to permit rational utilization of these agents. Methods: We have studied the effects of a range of endogenous and synthetic PPAR gamma ligands on proliferation, growth arrest (FACS analysis) and apoptosis (caspase-3/7 activation and DNA fragmentation) in multiple prostate carcinoma cell lines (DU145, PC-3 and LNCaP) and in a series of cell lines modelling metastatic transitional cell carcinoma of the bladder (TSU-Pr1, TSU-Pr1-B1 and TSU-Pr1-B2). Results: 15-deoxy-prostaglandin J(2) (15dPGJ2), troglitazone (TGZ) and to a lesser extent ciglitazone exhibited inhibitory effects on cell number; the selective PPAR. antagonist GW9662 did not reverse these effects. Rosiglitazone and pioglitazone had no effect on proliferation. In addition, TGZ induced G0/G1 growth arrest whilst 15dPGJ2 induced apoptosis. Conclusion: Troglitazone and 15dPGJ2 inhibit growth of prostate and bladder carcinoma cell lines through different mechanisms and the effects of both agents are PPAR gamma-independent.

Chan, S. W., et al. (2013). "Early detection of clinically significant prostate cancer at diagnosis: a prospective study using a novel panel of TMPRSS2: ETS fusion gene markers." Cancer Medicine 2(1): 63-75.

We explore noninvasive clinical applications of multiple disease-specific fusion markers recently discovered in prostate cancer to predict the risk of cancer occurrence and aggressiveness at diagnosis. A total of 92 men who were prostatespecific antigen (PSA) screened and scheduled for diagnostic biopsy were enrolled for this study. Prospectively collected urine was blind coded for laboratory tests. RNA from urine sediments was analyzed using a panel of 6 TMPRSS2:ETS fusion markers with a sensitive quantitative PCR platform. The pathology reported 39 biopsy-positive cases from 92 patients (42.4%). In urine test, 10 unique combinations of fusion types were detected in 32 of 92 (34.8%) prebiopsy samples. A novel combination of fusion markers, termed Fx (III, IV, ETS), was identified with a sensitivity of 51.3% and an odds ratio of 10.1 in detecting cancer on biopsy. Incorporating a categorical variable of Fx (III, IV, ETS) with urine PCA3 and serum PSA, a regression model was developed to predict biopsy outcomes with an overall accuracy of 77%. Moreover, the overexpression of Fx (III, IV, or ETS) was shown to be an independent predictor to the high-grade cancer, with a predictive accuracy of 80% when coupled with PSA density. The individualized risk scores further stratified a high-risk group that is composed of 92% high-grade cancers and a low-risk group that harbors mainly clinically insignificant cancers. In conclusion, we have identified a novel combination of fusion types very specific to the clinically significant prostate cancer and developed effective regression models to predict biopsy outcomes and aggressive cancers at diagnosis.

Chen, J., et al. (2013). "Identification, prioritization, and evaluation of glycoproteins for aggressive prostate cancer using quantitative glycoproteomics and antibody-based assays on tissue specimens." Proteomics 13(15): 2268-2277.

Prostate cancer is highly heterogeneous in nature; while the majority of cases are clinically insignificant, some cases are lethal. Currently, there are no reliable screening methods for aggressive prostate cancer. Since most established serum and urine biomarkers are glycoproteins secreted or leaked from the diseased tissue, the current study seeks to identify glycoprotein markers specific to aggressive prostate cancer using tissue specimens. With LC-MS/MS glycoproteomic analysis, we identified 350 glycopeptides with 17 being altered in aggressive prostate cancer. ELISA assays were developed/purchased to evaluate four candidates, that is, cartilage oligomeric matrix protein (COMP), periostin, membrane primary amine oxidase (VAP-1), and cathepsin L, in independent tissue sets. In agreement with the proteomic analysis, we found that COMP and periostin expressions were significantly increased in aggressive prostate tumors while VAP-1 expression was significantly decreased in aggressive tumor. In addition, the expression of these proteins in prostate metastases also follows the same pattern observed in the proteomic analysis. COMP and periostin and decrease in VAP-1 expression in the prostate may be associated with aggressive prostate cancer.

Chen, M., et al. (2011). "The Discovery of Putative Urine Markers for the Specific Detection of Prostate Tumor by Integrative Mining of Public Genomic Profiles." PloS one 6(12).

Urine has emerged as an attractive biofluid for the noninvasive detection of prostate cancer (PCa). There is a strong imperative to discover candidate urinary markers for the clinical diagnosis and prognosis of PCa. The rising flood of various omics profiles presents immense opportunities for the identification of prospective biomarkers. Here we present a simple and efficient strategy to derive candidate urine markers for prostate tumor by mining cancer genomic profiles from public databases. Prostate, bladder and kidney are three major tissues from which cellular matters could be released into urine. To identify urinary markers specific for PCa, upregulated entities that might be shed in exosomes of bladder cancer and kidney cancer are first excluded. Through the ontology-based filtering and further assessment, a reduced list of 19 entities encoding urinary proteins was derived as putative PCa markers. Among them, we have found 10 entities closely associated with the process of tumor cell growth and development by pathway enrichment analysis. Further, using the 10 entities as seeds, we have constructed a protein-protein interaction (PPI) subnetwork and suggested a few urine markers as preferred prognostic markers to monitor the invasion and progression of PCa. Our approach is amenable to discover and prioritize potential markers present in a variety of body fluids for a spectrum of human diseases.

Chen, Y.-b., et al. (2011). "Mesonephric Remnant Hyperplasia Involving Prostate and Periprostatic Tissue: Findings at Radical Prostatectomy." American Journal of Surgical Pathology 35(7): 1054-1061.

Mesonephric remnant hyperplasia is a very rare benign mimicker of prostate adenocarcinoma. As most reported cases are from transurethral resection specimens, the anatomic location and histologic spectrum of this entity have not been fully elucidated. Its immunohistochemical profile using current prostatic diagnostic markers has also not been well studied. In this study, we retrospectively characterized 10 cases of mesonephric remnant hyperplasia involving the prostate and periprostatic tissue, including 8 cases seen in radical prostatectomy specimens, with emphasis on the histopathologic and immunohistochemical features. Patients ranged in age from 48 to 70 years (average, 60 y). Seven of them had concurrent prostatic adenocarcinoma and underwent radical prostatectomy; one patient underwent prostatectomy because of the misdiagnosis of mesonephric remnant hyperplasia on transurethral resection as carcinoma; 2 patients had transurethral resection for urinary obstruction. The distribution of prostatic mesonephric hyperplasia was concentrated in 2 areas: one was in the anterior fibromuscular stroma and adjacent anterolateral periprostatic tissue (n = 6 of 8); the other was located toward the base posteriorly and posterolaterally either within or exterior to the prostate and around the seminal vesicle (n = 4 of 8). Histologic patterns observed included the following: small-to-medium-sized acini or tubules with a lobular distribution (n = 10 of 10); cysts either in clusters or scattered containing secretions (n = 8 of 10); small or ill-formed glands with an infiltrative growth (n = 7 of 10); glands with papillary infoldings or micropapillary tufts (n = 4 of 10); and 2 cases exceptionally displayed nodules of ill-formed small glands intermixed with spindle cells, mimicking sclerosing adenosis or Gleason pattern 5 prostate cancer. Most cases (7 of 10) had florid hyperplasia and harbored 3 or more growth patterns. All cases were negative for prostate-specific antigen. Cytokeratin 34 beta E12 was diffusely positive in 4 of 9 cases, and showed focal immunoreactivity in the remaining 5 cases. Except for focal positivity seen in 4 of 7 cases, p63 was largely negative. Racemase was focally positive in 4 of 7 cases. Small glands with an infiltrative growth pattern, the most difficult to distinguish from cancer, were negative (n = 3 of 6) or only focally positive (n = 3 of 6) for 34 beta E12, negative for p63 (n = 6 of 6), and focally positive for racemase (n = 4 of 6). All cases examined in the study were diffusely positive for PAX8. In conclusion, mesonephric remnant hyperplasia not only involves the bladder neck and base of the prostate as previously described, but may also present as a florid growth in the anterior fibromuscular stroma from the apex to the base, closely mimicking prostate cancer. Although basal cell marker and racemase expression overlaps with prostate cancer, mesonephric hyperplasia's unique morphology along with distinctive immunohistochemical expression of PAX8 and lack of prostate-specific antigen can help in distinguishing this benign entity from prostatic adenocarcinoma.

Cheng, F., et al. (2009). "Quantum-dot-based technology for sensitive and stable detection of prostate stem cell antigen expression in human transitional cell carcinoma." International Journal of Biological Markers 24(4): 271-276.

Quantum dots (QDs) as a biological labeling material for medical applications need to be evaluated for the sensitivity and stability of their fluorescence. Comparison of QD-based immunolabeling and commonly used immunohistochemical staining in detecting the expression of prostate stem cell antigen (PSCA) in bladder tumor tissues revealed that the two methods had similar sensitivity in the differential display of PSCA expression correlated with tumor stage and grade (kappa=0.92, p<0.001). In addition, the intensity of QD fluorescence remained stable for at least 10 days after conjugation to the PSCA protein and nearly 96% of the positive expression in samples lasted for one month. (Int J Biol Markers 2009; 24: 271-6)

Cho, S. Y., et al. (2012). "Biodistribution, Tumor Detection, and Radiation Dosimetry of F-18-DCFBC, a Low-Molecular-Weight Inhibitor of Prostate-Specific Membrane Antigen, in Patients with Metastatic Prostate Cancer." Journal of Nuclear Medicine 53(12): 1883-1891.

Prostate-specific membrane antigen (PSMA) is a type II integral membrane protein expressed on the surface of prostate cancer (PCa) cells, particularly in androgen-independent, advanced, and metastatic disease. Previously, we demonstrated that N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-F-18-fluorobenzyl-L-cysteine (F-18-DCFBC) could image an experimental model of PSMA-positive PCa using PET. Here, we describe the initial clinical experience and radiation dosimetry of F-18-DCFBC in men with metastatic PCa. Methods: Five patients with radiologic evidence of metastatic PCa were studied after the intravenous administration of 370 MBq (10 mCi) of F-18-DCFBC. Serial PET was performed until 2 h after administration. Time-activity curves were generated for selected normal tissues and metastatic foci. Radiation dose estimates were calculated using OLINDA/EXM 1.1, Results: Most vascular organs demonstrated a slow decrease in radioactivity concentration over time consistent with clearance from the blood pool, with primarily urinary radiotracer excretion. Thirty-two PET-positive suspected metastatic sites were identified, with 21 concordant on both PET and conventional imaging for abnormal findings compatible with metastatic disease. Of the 11 PET-positive sites not identified on conventional imaging, most were within the bone and could be considered suggestive for the detection of early bone metastases, although further validation is needed. The highest mean absorbed dose per unit administered radioactivity (mu Gy/MBq) was in the bladder wall (32.4), and the resultant effective dose was 19.9 +/- 1.34 mu Sv/MBq (mean +/- SD). Conclusion: Although further studies are needed for validation, our findings demonstrate the potential of F-18-DCFBC as a new positron-emitting imaging agent for the detection of metastatic PCa. This study also provides dose estimates for F-18-DCFBC that are comparable to those of other PET radiopharmaceuticals such as F-18-FDG.

Christensen, E., et al. (2008). "Practical approaches to proteomic biomarkers within prostate cancer radiotherapy trials." Cancer and Metastasis Reviews 27(3): 375-385.

Introduction Proteomic biomarkers may be useful for monitoring therapeutic response and to triage cancer patients to best therapy. Objectives In this review, we highlight the importance of specimen acquisition, preparation and analysis in radiotherapy proteomic studies. We also discuss practical approaches for the design and execution of clinical proteomic studies using our recent experience based on specimens accrued during prostate cancer radiation therapy. Discussion and Conclusions Numerous proteomic methods are being employed, including high-throughput mass spectrometry and immunoassays, and using solid tissues, blood and urine for analysis. Given the potential complexity of cytokine and other protein responses, there is a need to assess proteomic signatures within serial samples as longitudinal studies during a course of fractionated radiotherapy (RT).

Christensen, E., et al. (2009). "Longitudinal Cytokine Expression during IMRT for Prostate Cancer and Acute Treatment Toxicity." Clinical Cancer Research 15(17): 5576-5583.

Purpose: Proteomic profiling of patients undergoing intensity-modulated radiotherapy (IMRT) for prostate cancer can identify unique biomarkers that reflect acute toxicity in normal tissues. Our objectives were to measure inflammatory cytokine proteins during IMRT and assess the variability of individual proteomic signatures. Experimental Design: Forty-two patients with intermediate-risk prostate cancer were recruited as follows: group 1, definitive IMRT (78 Gy in 39 fractions, n = 22), and group 2, IMRT postprostatectomy (66 Gy in 33 fractions, n = 20). Blood/urine samples were collected at baseline and weekly during IMRT. Acute toxicity was graded weekly during radiotherapy using CTC-AE v3.0 criteria. Multiplexed immunoassays were used to quantify cytokines including granulocyte macrophage colony-stimulating factor, IFN-gamma, tumor necrosis factor-alpha, interleukin (IL)-1 alpha, IL-2, IL6, IL-8, IL-10, and IL-12p70. Results: We observed positive correlations between cytokine expression between serum and plasma, but not between serum/plasma and urine. The Mann-Whitney test showed a significant increase in IFN-gamma and IL-6 during IMRT (P = 0.0077, 0.0035). Increasing IL-2 and IL-1 expression were associated with increased probability of acute gastrointestinal and genitourinary toxicity, respectively. Conclusions: Determination of radiation-response signatures is feasible using multiplexed immunoassays and is a promising predictive early biomarker of toxicity outcomes. (Clin Cancer Res 2009;15(17):5576-83)

Christiansen, H., et al. (2007). "Increase of hepcidin plasma and urine levels is associated with acute proctitis and changes in hemoglobin levels in primary radiotherapy for prostate cancer." Journal of Cancer Research and Clinical Oncology 133(5): 297-304.

Purpose To analyse hepcidin serum and urine levels during radiotherapy for prostate cancer. Methods In 18 patients undergoing radiotherapy for prostate cancer, blood, plasma, and urine samples were taken before and during radiotherapy. Complete blood cell count, pro-hepcidin-, ferritin-, transferrin-, IL-1 beta-, IL-6-, and TNF-alpha concentration was determined. Pro-hepcidin concentration was additionally measured in urine samples. Toxicity was evaluated weekly. Differences among tested factors were tested by Wilcoxon rank sign test for paired data. Results In ten patients developing acute radiation-induced proctitis, a significant increase in pro-hepcidin, IL-6, and TNF-alpha plasma levels (p < 0.05) was detected. Pro-hepcidin urine levels also showed a strong trend towards increase (p = 0.06). Concurrently, hemoglobin, and leucocytes were significantly decreased in the patients with acute proctitis (p < 0.05). In eight patients showing no symptoms of proctitis, solely a significant decrease for leucocytes was detected. Additive, these patients showed a significant increase of ferritin, and a decrease of transferrin levels (p < 0.05). Conclusions Hepcidin levels are increased and hemoglobin is decreased during radiotherapy for prostate cancer in patients who develop acute proctitis. Radiation-induced expression of cytokines may be responsible for increased hepcidin expression in the liver. Regulation of iron metabolism by hepcidin may be an underestimated response in radiotherapy.

Cintra, H. S., et al. (2013). "Investigation of Genetic Polymorphisms Related to the Outcome of Radiotherapy for Prostate Cancer Patients." Disease Markers: 701-710.

The purpose of this study was to evaluate the association between ATM, TP53 and MDM2 polymorphisms in prostate cancer patients and morbidity after radiotherapy. The presence of ATM (rs1801516), TP53 (rs1042522, rs1800371, rs17878362, rs17883323, and rs35117667), and MDM2 (rs2279744) polymorphisms was assessed by direct sequencing of PCR fragments from 48 patients with histologically proven prostate adenocarcinoma and treated with external beam radiation. The side effects were classified according to the Radiation Therapy Oncology Group (RTOG) score. The results showed no association between clinical characteristics and the development of radiation toxicities (P > 0.05). The C>T transition in the position 16273 (intron 3) of TP53 (rs35117667) was significantly associated with the risk of acute skin toxicity (OR: 0.0072, 95% CI 0.0002-0.227, P = 0.003). The intronic TP53 polymorphism at position 16250 (rs17883323) was associated with chronic urinary toxicity (OR: 0.071, 95% CI 0.006-0.784, P = 0.032). No significant associations were found for the remaining polymorphisms (P > 0.05). The results show that clinical characteristics were not determinant on the developing of radiation sensitivity in prostate cancer patients, and intronic TP53 polymorphisms would be associated with increased acute and chronic radiation toxicities. These observations corroborate the importance of investigating the genetic profile to predict adverse side effects in patients undergoing radiotherapy.

Comeglio, P., et al. (2014). "Opposite Effects of Tamoxifen on Metabolic Syndrome-Induced Bladder and Prostate Alterations: A Role for GPR30/GPER?" Prostate 74(1): 10-28.

BACKGROUNDBPH and LUTS have been associated to obesity, hypogonadism, and metabolic syndrome (MetS). MetS-induced prostate and bladder alterations, including inflammation and tissue remodeling, have been related to a low-testosterone and high-estrogen milieu. In addition to ERs, GPR30/GPER is able to mediate several estrogenic non-genomic actions. METHODSSupplementing a subgroup of MetS rabbits with tamoxifen, we analyzed the in vivo effects on MetS-induced prostate and bladder alterations. The effects of selective ER/GPER ligands and GPER silencing on prostate inflammation were also studied in vitro using hBPH cells. RESULTSER, ER, and PR expression was upregulated in MetS bladder, where tamoxifen decreased ER and PR expression, further stimulating ER. In addition, tamoxifen-dosing decreased MetS-induced overexpression of inflammatory and tissue remodeling genes. In prostate, sex steroid receptors, pro-inflammatory and pro-fibrotic genes were upregulated in MetS. However, tamoxifen did not affect them and even increased COX-2. In hBPH cells, 17-estradiol increased IL-8 secretion, an effect blunted by co-treatment with GPER antagonist G15 but not by ER antagonist ICI 182,780, which further increased it. GPER agonist G1 dose-dependently (IC50=1.6nM) induced IL-8 secretion. In vitro analysis demonstrated that GPER silencing reverted these stimulatory effects. CONCLUSIONSGPER can be considered the main mediator of estrogen action in prostate, whereas in bladder the mechanism appears to rely on ER, as indicated by in vivo experiments with tamoxifen dosing. Limiting the effects of the MetS-induced estrogen action via GPER could offer new perspectives in the management of BPH/LUTS, whereas tamoxifen dosing showed potential benefits in bladder. Prostate 74:10-28, 2014. (c) 2013 Wiley Periodicals, Inc.

Corcoran, C., et al. (2014). "miR-34a is an Intracellular and Exosomal Predictive Biomarker for Response to Docetaxel with Clinical Relevance to Prostate Cancer Progression." Prostate 74(13): 1320-1334.

BACKGROUND. Docetaxel-resistance limits successful treatment of castration resistant prostate cancer. We previously demonstrated that extracellular vesicles (exosomes) may play a role in regulating docetaxel resistance. Here, we investigated intracellular and extracellular (exosomal) miRNAs related to docetaxel resistance. METHODS. Following global miRNA profiling of cell line models of docetaxel-resistance and their corresponding exosomes, we investigated the clinical relevance of four selected miRNAs (miR-598, miR-34a, miR-146a, miR-148a) in four publically available clinical cohorts representing both primary and advanced disease in tissue and urine specimens. One of these miRNAs, miR-34a was selected for functional evaluation by miRNA inhibition and over-expression in vitro. We further assessed the panel of miRNAs for their combined clinical relevance as a biomarker signature by examining their common predicted targets. RESULTS. A strong correlation was found between the detection of miRNAs in exosomes and their corresponding cells of origin. Of the miRNAs chosen for further validation and clinical assessment, decreased miR-34a levels showed substantial clinical relevance and so was chosen for further analysis. Manipulating miR-34a in prostate cancer cells confirms that this miRNA regulates BCL-2 and may, in part, regulate response to docetaxel. When combined, these miRNAs are predicted to regulate a range of common mRNA targets, two of which (e. g., SNCA, SCL7A5) demonstrate a strong relationship with prostate cancer progression and poor prognosis. CONCLUSIONS. This study supports the extracellular environment as an important source of minimally invasive predictive biomarkers representing their cellular origin. Using miR-34a as example, we showed that biomarkers identified in this manner may also hold functional relevance. (C) 2014 The Authors. The Prostate, published byWiley Periodicals, Inc.

Cornu, J.-N., et al. (2013). "Urine TMPRSS2:ERG fusion transcript integrated with PCA3 score, genotyping, and biological features are correlated to the results of prostatic biopsies in men at risk of prostate cancer." Prostate 73(3): 242-249.

BACKGROUND Detection of fusion gene TMPRSS2:ERG transcripts in urine have been recently described in order to refine urine-based detection of prostate cancer (PCa), but data its clinical impact remain scarce. We aimed at investigating the correlation of TMPRSS2:ERG, prostate cancer antigen 3 (PCA3), prostate specific antigen (PSA) density, genetic variants, and androgenic status with outcome and pathological findings at prostatic biopsy. METHODS Between 2007 and 2011, 291 patients at risk of PCa because of PSA?>?3.0?ng/ml (55%) or candidate to active surveillance protocol justifying restaging biopsy management (45%) were recruited. TMPRSS2:ERG was detected by urine assay (Progensa (TM)). PCA3-score, PSA level, bioavailable testosterone level, prostate volume, rs1447295 and rs6983267 genotypes were prospectively assessed. Univariate and multivariate analysis by logistic regression model (logit) were conducted to study the correlation of TMPRSS2:ERG status, PCA3, and PSA density with biopsy results, and Gleason score. RESULTS Of 291 patients, 173 had PCa and 118 had negative biopsy. PCA3 score, PSA density and TMPRSS2:ERG-score were correlated with presence of PCa (P?<?0.0001, P?=?0.046, and P?<?0.0001, respectively). This correlation remained strong on multivariable analysis model (area under curve 0.743). PCA3 score and PSA density were significantly associated with presence of Grade 4 through multivariable analysis. PCA3 score was also correlated to the percentage of positive cores at biopsy (P?=?0.008). CONCLUSIONS Integration of levels TMPRSS2:ERG transcripts in urine, with PCA3-score, androgenic status, genetic status and traditional clinical variables could significantly increase detection of high risk localized PCa. Prostate 73: 242249, 2013. (c) 2012 Wiley Periodicals, Inc.

Culig, Z. (2014). "Distinguishing indolent from aggressive prostate cancer." Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer 202: 141-147.

Prostate cancer natural course is variable and it is difficult to determine prognosis on the basis of limited clinical information. In order to distinguish between aggressive and indolent tumors, genomic analysis, proteomic studies, and biomarker measurement were applied. Identification of single nucleotide polymorphisms may help to assess prostate cancer risk, however, it is questionable whether single nucleotide polymorphisms may predict a good or bad prognosis. Results of genomic and proteomic analyses between different laboratories may be difficult to compare because of non-standardized procedures which may be responsible for variant results. One of the early changes in prostate tumor tissues which may indicate a bad prognosis is high phosphorylation of Akt. A biomarker which is specific for prostate cancer is the TMPRSS2-ERG fusion which occurs in about 50% of tumors. Experimental studies indicate that this gene fusion may promote malignant phenotype. Biomarkers which could distinguish between latent and aggressive tumors may be detected in prostate tissue, serum, and urine. In summary, there is a limited progress in the field of prognostic biomarkers because of prostate cancer heterogeneity and missing unification of diagnostic procedures.

Czifra, G., et al. (2009). "Increased expressions of cannabinoid receptor-1 and transient receptor potential vanilloid-1 in human prostate carcinoma." Journal of Cancer Research and Clinical Oncology 135(4): 507-514.

Recently, functional cannabinoid receptor-1 (CB1) and vanilloid receptor-1 (TRPV1) have been described in human prostate and prostate cancer-derived cell lines where the activation of the receptors resulted in inhibition of cellular growth. We, however, lack the description of the expression of these molecules in human prostate cancer (PCC) and in benign prostate hyperplasia (BPH). Therefore, immunohistochemistry, Western blotting, and quantitative "real-time Q-PCR were performed to define the expressions of CB1 and TRPV1 in healthy and diseased prostate tissues. CB1 was identified in epithelial and smooth muscle cells types of the human prostate, whereas TRPV1 was exclusively localized to the mucosal cells. We also found that the expression of CB1 and TRPV1 (both at the protein and mRNA levels) were significantly up-regulated in PCC. However, while the increased expression of TRPV1 showed a proper correlation with increasing PCC tumor grades, such phenomenon was not observed with CB1. In addition, we also measured markedly elevated CB1 levels in BPH tissues whilst the expression of TRPV1 was not altered when compared to healthy control prostate. Our findings strongly argue for that (1) the CB1 and TRPV1 molecules as well as their ligands may indeed possess a promising future role in the treatment of PCC; (2) TRPV1 may also serve as a prognostic factor in PCC; and (3) CB1 may act as a potential target molecule in the therapeutic management of BPH.

Damaraju, S., et al. (2006). "Association of DNA repair and steroid metabolism gene polymorphisms with clinical late toxicity in patients treated with conformal radiotherapy for prostate cancer." Clinical Cancer Research 12(8): 2545-2554.

Objective: To explore the possible relationship between single nucleotide polymorphisms (SNP) in candidate genes encoding DNA damage recognition/repair/response and steroid metabolism proteins with respect to clinical radiation toxicity in a retrospective cohort of patients previously treated with three-dimensional conformal radiotherapy (3-DCRT) for prostate cancer. Experimental Design: One hundred twenty-four patients with prostate cancer underwent 3-DCRT at our institution between September 1996 and December 2000. Of these, 83 consented for follow-up of blood sampling and SNP analysis. Twenty-eight patients were documented as having experienced grade >= 2 late bladder or rectal toxicity (scoring system of Radiation Therapy Oncology Group) on at least one follow-up visit. We analyzed 49 SNPs in BRCA1, BRCA2, ESR1, XRCC1, XRCC2, XRCC3, NBN, RAD51, RAD52, LIG4, ATM, BCL2, TGFB1, MSH6, ERCC2, XPF NR3C1, CYP1A1, CYP2C9, CYP2C19, CYP3A5, CYP2D6, CYP11B2, and CYP17A1 genes using the Pyrosequencing technique. Results: Significant univariate associations with late rectal or bladder toxicity (grade >= 2) were found for XRCC3 (A)G 5' untranslated region NT 4541), LIG4 (T>C Asp (568)Asp), MLH1 (C)T, Val(219)Ile), CYP2D6*4 (G>A splicing defect), mean rectal and bladder dose, dose to 30% of rectum or bladder, and age <60 years. On Cox multivariate analysis, significant associations with toxicity were found for LIG4 (T>C, Asp(568)Asp), ERCC2 (G>A, Asp(711)Asp), CYP2D6*4 (G>A, splicing defect), mean bladder dose >60 Gy, and dose to 30% of rectal volume >75 Gy. Conclusions: In this study, we identified SNPs in LIG4, ERCC2, and CYP2D6 genes as putative markers to predict individuals at risk for complications arising from radiation therapy in prostate cancer.

Davalieva, K., et al. (2015). "Proteomics analysis of urine reveals acute phase response proteins as candidate diagnostic biomarkers for prostate cancer." Proteome Science 13.

Despite the overall success of prostate specific antigen (PSA) in screening and detection of prostate cancer (PCa), its use has been limited due to the lack of specificity. The principal driving goal currently within PCa research is to identify non-invasive biomarker(s) for early detection of aggressive tumors with greater sensitivity and specificity than PSA. In this study, we focused on identification of non-invasive biomarkers in urine with higher specificity than PSA. We tested urine samples from PCa and benign prostatic hyperplasia (BPH) patients by 2-D DIGE coupled with MS and bioinformatics analysis. Statistically significant (p < 0.05), 1.8 fold variation or more in abundance, showed 41 spots, corresponding to 23 proteins. The Ingenuity Pathway Analysis showed significant association with the Acute Phase Response Signaling pathway. Nine proteins with differential abundances were included in this pathway: AMBP, APOA1, FGA, FGG, HP, ITIH4, SERPINA1, TF and TTR. The expression pattern of 4 acute phase response proteins differed from the defined expression in the canonical pathway. The urine levels of TF, AMPB and HP were measured by immunoturbidimetry in an independent validation set. The concentration of AMPB in urine was significantly higher in PCa while levels of TF and HP were opposite (p < 0.05). The AUC for the individual proteins ranged from 0.723 to 0.754. The combination of HP and AMBP yielded the highest accuracy (AUC = 0.848), greater than PSA. The proposed biomarker set is quickly quantifiable and economical with potential to improve the sensitivity and specificity of PCa detection.

Defilippi, E., et al. (2011). "Alternative tests to PSA for prostate cancer diagnosis." Urologia 78(2): 75-81.

Prostate specific antigen (PSA) is still the most useful tool to select the population requiring prostatebiopsy. The main downsides of PSA are an inadequate sensitivity to be used in screening and a low specificity for cancer detection. So far, a limited value for PSA derivates (velocity, density, free, proisoforms and doubling time) has been recognised. We present a short review of the literature describing a selection of the most promising alternatives to PSA being studied currently: PCA3, serum kallikreins, serum detectable prostate specific membrane antigen, the nuclear matrix protein EPCA, EPCA-2, prostatic acid phosphatase, urine detectable GSTP1, anti-AMACR antibodies, sarcosine, plasminogen activating urokinase, IGFBP, TGF beta 1,PSP94, IL6, plasmatic DNA, serum autoantibodies, neuroendocrine markers, proteomic analysis.

Dhillon, P. K., et al. (2009). "Aberrant Cytoplasmic Expression of p63 and Prostate Cancer Mortality." Cancer Epidemiology Biomarkers & Prevention 18(2): 595-600.

Protein expression of p63 is used to differentiate prostate cancer from benign mimickers. Recent studies suggest that it may also distinguish aggressive prostate cancer with down-regulated expression occurring in men with more advanced disease. We conducted a prospective study among 298 men ages 51 to 84 years who were diagnosed with prostate cancer in the Physicians' Health Study in 1983 to 2004 and whose tissue was available for immunohistochemical staining. We used Cox proportional hazards regression to evaluate the association of p63 protein expression with fatal prostate cancer. We correlated p63 expression with tumor cell proliferation (Ki-67) and apoptosis (TUNEL staining). The predominant location of tumor p63 staining occurred in the cytoplasm, an uncommon departure from the strong nuclear staining usually observed in nonneoplastic basal cells. Increasing expression of cytoplasmic p63 (tertiles) was associated with prostate cancer mortality (n = 19 deaths); the hazard ratios (95% confidence intervals) were 1.0 (reference), 4.0 (0.9-18.9), and 5.9 (1.3-27.5; P(trend) = 0.03). The positive trend remained significant (P = 0.047) after multivariable adjustment for age, year of diagnosis, and Gleason score. Higher tertiles of cytoplasmic p63 were also associated with reduced levels of apoptosis (P(trend) = 0.0408) and increased cellular proliferation (P(trend) = 0.0026). We found aberrant expression of p63 in the cytoplasm to be associated with increased prostate cancer-specific mortality up to 20 years after diagnosis. The mislocalized expression was associated with reduced apoptosis and higher proliferative activity and may suggest an oncogenic role in prostate cancer progression and survival. (Cancer Epidemiol Biomarkers Prev 2009;18(2):595-600)

Dijkstra, S., et al. (2014). "Prostate Cancer Biomarker Profiles in Urinary Sediments and Exosomes." Journal of Urology 191(4): 1132-1138.

Purpose: Urinary biomarker tests for diagnosing prostate cancer have gained considerable interest. Urine is a complex mixture that can be subfractionated. We evaluated 2 urinary fractions that contain nucleic acids, ie cell pellets and exosomes. The influence of digital rectal examination before urine collection was also studied and the prostate cancer specific biomarkers PCA3 and TMPRSS2-ERG were assayed. Materials and Methods: Urine samples were prospectively obtained before and after digital rectal examination from 30 men scheduled for prostate biopsy. Cell pellet and exosomes were isolated and used for biomarker analysis. Analytical and diagnostic performance was tested using the Student t-test and ROC curves. Results: Unlike the exosome fraction, urinary sediment gene expression analysis was compromised by amorphous precipitation in 10% of all specimens. Digital rectal examination resulted in increased mRNA levels in each fraction. This was particularly relevant for the exosomal fraction since after digital rectal examination the number of samples decreased in which cancer specific markers were below the analytical detection limit. Biomarker diagnostic performance was comparable to that in large clinical studies. In exosomes the biomarkers had to be normalized for prostate specific antigen mRNA while cell pellet absolute PCA3 levels had diagnostic value. Conclusions: Exosomes have characteristics that enable them to serve as a stable substrate for biomarker analysis. Thus, digital rectal examination enhances the analytical performance of biomarker analysis in exosomes and cell pellets. The diagnostic performance of biomarkers in exosomes differs from that of cell pellets. Clinical usefulness must be prospectively assessed in larger clinical cohorts.

Dijkstra, S., et al. (2014). "Clinical use of novel urine and blood based prostate cancer biomarkers: A review." Clinical Biochemistry 47(10-11): 889-896.

In the era of upcoming techniques for molecular profiling, breakthroughs led to new discoveries in the field of prostate cancer (PCa) biomarkers. Since the early 1990s a tremendous increase in PCa incidence is seen, dedicated to the introduction of prostate specific antigen (PSA) testing. However, due to its lack of specificity many men undergo unnecessary biopsies, resulting in a rising incidence of clinically insignificant PCa. To overcome this drawback, cancer specific biomarkers are needed to identify patients who are at high risk of harbouring PCa and to distinguish patients with aggressive disease from patients with insignificant cancer. The most noninvasive, easy to obtain substrate for biomarker measurement is urine. The most promising markers to date are PCA3 and TMPRSS2-ERG. Both markers demonstrate to have a higher specificity and diagnostic accuracy for PCa outcome compared to serum PSA. This might better predict the presence of PCa and therefore reduce the number of unnecessary biopsies. Combining both markers in a panel might result in an even higher diagnostic accuracy, given the heterogeneity of the disease. In PCa management, circulating tumour cells (CTCs) detected in the blood seem a promising tool to predict treatment response and survival benefit Although results appear to be encouraging, the biggest challenge about new markers in PCa is to validate them in large clinical trials and subsequently implement these markers into clinical practice. In this review we discuss the clinical usefulness of novel, noninvasive tests in PCa management. (C) 2013 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Djavan, B., et al. (2011). "Diagnostic Strategies for Prostate Cancer." European Urology Supplements 10(3): E26-E37.

Context: Prostate cancer (PCa) is the most common malignancy in men in westernized cultures and the incidence of PCa is rapidly rising in low-risk countries due to significant westernization in these populations. Prostate-specific antigen (PSA) is the gold standard for screening of PCa. Means to improve the specificity and sensitivity of this screening method are imperative. Objective: In this article, we review novel blood-, urine-, and tissue-based bio-markers for screening and early diagnosis of PCa. Evidence acquisition: We discuss three studies: the 2001 Tyrol study, the European Randomized Study of Screening for Prostate Cancer (ERSPC), and the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Evidence synthesis: The new molecular forms of PSA, or precursor isoforms (pPSA), are exciting, but further studies are required to validate their clinical application. Measurement of p2PSA, benign PSA (bPSA), and intracellular macrophage PSA (imPSA) proved to be more stable and promising compared to free PSA and serum total PSA, thus improving early diagnosis of PCa, especially in patients with low serum PSA levels. Novel approaches in molecular technology seem to overcome hurdles in detecting PCa cells and markers in urinary samples. Recent results revealed the proteins PCA3 and AMACR to be useful and efficient new tools for PCa detection. PSA density and PSA velocity are certainly superior to a single PSA measurement, and PCa risk calculators may further enhance cancer prediction. Conclusions: The use of PSA has led to overdiagnosis and overtreatment of PCa, resulting in controversy about its use for screening. PSA also has limited accuracy and poor specificity for early detection of PCa. Novel markers for PCa detection, staging, and monitoring are required. Published by Elsevier B.V. on behalf of European Association of Urology.

Downes, M. R., et al. (2006). "Application of proteomic strategies to the identification of urinary biomarkers for prostate cancer: A review." Biomarkers 11(5): 406-416.

In the post-genomic era, genes and proteins are now studied on a more comprehensive scale. Studying disease processes at only the genetic or transcriptomic level will give an incomplete amount of information. A proteomic approach potentially allows for a more global overview of how disease processes affect the proteins present in cells, tissues and organisms. The challenge arises in determining which proteins are affected in specific diseases and establishing which of these changes are unique to a particular disease. Existing and emerging proteomic technologies allow for high throughput analysis of proteins in a variety of sample types. Prostate cancer is a significant male health problem in the Western world. It is widely accepted that more specific prognostic and diagnostic markers of prostate cancer are urgently required. The present paper suggests that urine may be an attractive biofluid in which to pursue the identification of novel biomarkers of prostate cancer. This review introduces some proteomic techniques including mass spectrometry and the newer, quantitative proteomic strategies. It focuses on the potential application of these platforms to novel urinary biomarker identification in prostate malignancy. It also includes a synopsis of the current literature on urinary proteomics.

Downes, M. R., et al. (2007). "Urinary markers for prostate cancer." Bju International 99(2): 263-268.

Prostate cancer is the commonest solid-organ malignancy to affect men in Europe and the USA; it is estimated that one in six men will develop this cancer in their lifetime. Current screening relies on a digital rectal examination with a serum prostate-specific antigen test. Novel urinary diagnostic tests are potentially interesting screening tools for this disease. We examined published reports assessing the use of urinary markers for the diagnosis of prostate cancer. Using a PubMed-based search we identified studies of urinary markers for prostate cancer published from 1985 to February 2006 using the search terms 'urine', 'marker' and 'prostate cancer'. Studies to date have used small cohorts and relied on prostatic biopsies to provide histology. The sensitivity and specificity of markers are wide ranging but with only a few studies published on each putative marker it is difficult to assess their potential impact. Using urinary biomarkers for prostate cancer is a relatively novel diagnostic approach; they are appealing as a screening test because they are not invasive. Further work is needed to identify and validate 'signature markers' indicative of prostatic malignancy. The newer proteomic platforms are promising biomarker discovery tools that might uncover the next generation of urinary biomarkers.

Drake, R. R. and T. Kislinger (2014). "The proteomics of prostate cancer exosomes." Expert review of proteomics 11(2): 167-177.
Exosomes and other microvesicles are emerging as rich reservoirs of tumor-specific proteins and biomarkers for cancer detection and progression. For prostate cancer, exosomes secreted by the prostate can be isolated from prostatic secretions, seminal fluid, tissue, urine or blood for further proteomic analysis. Structurally, prostate-derived exosomes are distinct in size, membrane composition and specific prostate protein content, potentially providing a novel and easily isolatable source of biomarkers from clinical biofluids. The key to these isolation strategies will be the targeting of specific prostatic proteins expressed in these exosomes, thus requiring detailed proteomic characterizations. A summary of ongoing efforts to characterize the proteome of these unique prostate cancer-associated exosomes and their potential applications for use in biomarker assays is presented.

Dudderidge, T. J., et al. (2010). "Diagnosis of prostate cancer by detection of minichromosome maintenance 5 protein in urine sediments." British Journal of Cancer 103(5): 701-707.
BACKGROUND: The accuracy of prostate-specific antigen (PSA) testing in prostate cancer detection is constrained by low sensitivity and specificity. Dysregulated expression of minichromosome maintenance (Mcm) 2-7 proteins is an early event in epithelial multistep carcinogenesis and thus MCM proteins represent powerful cancer diagnostic markers. In this study we investigate Mcm5 as a urinary biomarker for prostate cancer detection. METHODS: Urine was obtained from 88 men with prostate cancer and from two control groups negative for malignancy. A strictly normal cohort included 28 men with complete, normal investigations, no urinary calculi and serum PSA <2 ngml(-1). An expanded control cohort comprised 331 men with a benign final diagnosis, regardless of PSA level. Urine was collected before and after prostate massage in the cancer patient cohort. An immunofluorometric assay was used to measure Mcm5 levels in urine sediments. RESULTS: The Mcm5 test detected prostate cancer with 82% sensitivity (confidence interval (CI) 72-89%) and with a specificity ranging from 73 (CI=68-78%) to 93% (CI=76-99%). Prostate massage led to increased Mcm5 signals compared with pre-massage samples (median 3440 (interquartile range (IQR) 2280 to 5220) vs 2360 (IQR <1800 to 4360); P=0.009), and was associated with significantly increased diagnostic sensitivity (82 vs 60%; P=0.012). CONCLUSIONS: Urinary Mcm5 detection seems to be a simple, accurate and noninvasive method for identifying patients with prostate cancer. Large-scale prospective trials are now required to evaluate this test in diagnosis and screening. British Journal of Cancer (2010) 103, 701-707. doi:10.1038/sj.bjc.6605785 www.bjcancer.com Published online 20 July 2010 (C) 2010 Cancer Research UK

Duijvesz, D., et al. (2011). "Exosomes as Biomarker Treasure Chests for Prostate Cancer." European Urology 59(5): 823-831.

Context: Although progress has been made with regard to types of markers (protein, DNA, RNA, and metabolites) and implementation of improved technologies (mass spectrometry, arrays, and deep sequencing), the discovery of novel biomarkers for prostate cancer (PCa) in complex fluids, such as serum and urine, remains a challenge. Meanwhile, recent studies have reported that many cancer-derived proteins and RNAs are secreted through small vesicles known as exosomes. Objective: This narrative review describes recent progress in exosome research, focusing on the potential role of exosomes as novel biomarkers for PCa. The purpose of this review is to acquaint clinicians and researchers in the field of urology with the potential role of exosomes as biomarker treasure chests and with their clinical value. Evidence acquisition: Medline and Embase entries between 1966 and September 2010 were searched using the keywords exosomes, microvesicles, prostasomes, biomarkers, prostate cancer, and urology. Leading publications and articles constructively contributing to exosome research were selected for this review. Evidence synthesis: Exosomes are small vesicles (50-100 nm) secreted by almost all tissues; they represent their tissue origin. Purification of prostate- and PCa-derived exosomes will allow us to profile exosomes, providing a promising source of protein and RNA biomarkers for PCa. This profiling will contribute to the discovery of novel markers for the early diagnosis and reliable prognosis of PCa. Conclusions: Although the initial results are promising, further investigations are required to assess the clinical value of these exosomes in PCa. (C) 2010 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Dumache, R., et al. (2010). "Clinical applications of molecular biomarkers in prostate cancer detection." Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 114(2): 470-475.

Prostate cancer is a heterogeneous disease with regard to molecular alterations and clinical course. Early diagnosis of prostate cancer can increase the curative success rate for this disease. Because of the recent developments in the field of molecular biology, an increased interest occurred for molecular biomarkers, as tools for early prostate cancer detection, monitoring disease progression, predicting disease recurrence and therapeutic treatment efficacy. Many molecular biomarkers have been discovered in human serum, urine, seminal fluid and histological specimens.

Durand, X., et al. (2011). "Progensa (TM) PCA3 test for prostate cancer." Expert Review of Molecular Diagnostics 11(2): 137-144.

The lack of accuracy from typical prostate cancer diagnostic tools led us to investigate new biomarkers. Prostate cancer gene 3 (PCA3 or DD3) is a promising urinary biomarker of prostate cancer. This specific noncoding mRNA is highly overexpressed in more than 95% of primary prostate tumors. The feasibility of a PCA3 gene-based molecular assay based on the detection of prostate cancer cells in urine has been demonstrated, and a quantitative PCA3 urine test with the potential for general use in clinical settings was developed; the Progensa (TM) (Gen-Probe Inc., San Diego, CA, USA) PCA3 urine test. Current data from the literature demonstrate the superiority of the PCA3 score over prostate-specific antigen, in terms of predictive value and specificity, albeit with a slightly lower sensitivity. These results are particularly encouraging for the specific population of patients who have a first negative biopsy, as a PCA3 assay could avoid unnecessary repeated biopsies. Furthermore, limited data have investigated a correlation between PCA3 scores and tumor volumes, as well as an ability to distinguish indolent from significant cancer. In the near future, combinations of multiple biomarkers integrating PCA3 will optimize the detection and characterization of prostate cancer.

Durand, X., et al. (2010). "Urinary biomarkers in prostate cancer: An update." Progres En Urologie 20(13): 1184-1191.

Widespread screening for prostate cancer has led to an increased incidence, an improved disease specific survival, but also to overdiagnosis and overtreatment. The limitations of screening tools, especially PSA, have led to active investigation of new biomarkers in recent years. Urinary markers, suitable for large scale use, minimally invasive collected, arouse of particular interest. Numerous protein, DNA or RNA markers are explored in order to improve detection and prognostic evaluation of prostate cancer. Some of them have already shown clinical values. PCA3 provided particularly encouraging results for the specific population of patients having a first set of negative biopsy, for which using PCA3 assay could allow to avoid unnecessary repeated biopsy. Fusion genes showed promising abilities in prostate cancer detection. New research methods are also emerging, and high-throughput technologies will facilitate high-dimensional biomarker discovery. Future approaches will probably integrate proteomic, transcriptomic and multiplex approaches to identify combinations of multiple biomarkers to optimize the detection of prostate cancer. In the near future, these markers would probably be able to provide prognostic data to discriminate significant cancers, a major challenge for prostate cancer treatment. (c) 2010 Published by Elsevier Masson SAS.

Duskova, K. and S. Vesely (2015). "Prostate Specific Antigen. Current clinical application and future prospects." Biomedical Papers-Olomouc 159(1): 18-26.

Background. Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland and its production can be enhanced in benign and malignant diseases. The introduction of PSA testing has greatly increased the detection of prostate cancer. However there is continuing controversy and confusion over the most appropriate application of the PSA test. Methods. PubMed and Web of Science databases were used to search original and review articles on the historical aspects, clinical utilization and possible future directions in PSA. Conclusions. After its discovery, PSA was quickly established as an exquisitely sensitive tumor marker for prostate cancer detection, assessment of treatment responses and follow-up among patients with prostate cancer. Nevertheless, controversy exists about the proper threshold for recommending prostate biopsy. If this limit is lowered to improve the sensitivity even more, patients with low-risk prostate cancer would be subsequently detected. Post-treatment PSA levels can certainly provide valuable information about the effectiveness of the therapy given. Recently introduced ultrasensitive PSA detection techniques are offering new insight into the changes in serum PSA at very low concentrations. This has resulted in identification of valuable postoperative prognostic variables together with the possibility of earlier cancer relapse detection. The development of assays that may show superior sensitivity and specificity in prostate cancer diagnosis is focused on proteins possibly complexed with PSA and other potential markers detectable both in serum and urine. The goal of newly discovered prostate cancer biomarkers is greater cancer specificity in order to reduce the overdiagnosis, overtreatment and financial cost.

Elsamman, E., et al. (2006). "Prostate stem cell antigen predicts tumour recurrence in superficial transitional cell carcinoma of the urinary bladder." Bju International 97(6): 1202-1207.

Objectives To evaluate the relationship between prostate stem cell antigen (PSCA) expression level in transitional cell carcinoma (TCC) of the urinary bladder and various clinicopathological features, including stage and grade; and to determine whether PSCA mRNA expression predicts disease recurrence in superficial (not muscle-invasive) TCC of the bladder. Patients and Methods Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) was performed on 97 TCC tissue samples and in 36 samples of normal bladder urothelium; the findings were analysed in relation to clinicopathological factors. Immunohistochemical expression was examined using light and confocal immunofluorescence microscopy to validate the RT-PCR data. Results Twenty-seven patients developed disease recurrence, while the remaining 22 had no evidence of recurrence of superficial TCC of the bladder. There was significantly higher PSCA mRNA expression in TCC than in normal urothelium samples (P = 0.008). Superficial (TaT1) tumours had significantly higher PSCA expression than muscle-invasive (>= pT2) tumours (P < 0.001). There was no significant difference between patients with G1-2 tumours and those with G3 tumours (P = 0.109). Immunohistochemical analysis showed markedly greater PSCA expression in superficial than invasive TCC. Notably, from a multivariate analysis, the expression level of PSCA was an independent predictor of disease recurrence in superficial TCC (P = 0.012). Conclusions These findings suggest that the PSCA expression level measured by real-time RT-PCR could be a valuable prognostic marker for tumour recurrence in superficial TCC of the bladder.

Fachal, L., et al. (2012). "Association of a XRCC3 polymorphism and rectum mean dose with the risk of acute radio-induced gastrointestinal toxicity in prostate cancer patients." Radiotherapy and Oncology 105(3): 321-328.

Background and purpose: We have performed a case-control study among prostate cancer patients treated with three-dimensional conformational radiotherapy (3D-CRT) in order to investigate the association between single nucleotide polymorphisms (SNPs), treatment and patient features with gastrointestinal and genitourinary acute toxicity. Material and methods: A total of 698 patients were screened for 14 SNPs located in the ATM, ERCC2, LIG4, MLH1 and XRCC3 genes. Gastrointestinal and genitourinary toxicities were recorded prospectively using the Common Terminology Criteria for Adverse Events v3.0. Results: The XRCC3 SNP rs1799794 (G/G OR = 5.65; 95% CI: 1.95-16.38; G/A OR = 2.75; 95% CI: 1.25-6.05; uncorrected p-value = 2.8 x 10(-03); corrected p-value = 0.03; FDR q-value = 0.06) as well as the mean dose received by the rectum (OR= 1.06; 95% CI: 1.02-1.1; uncorrected p-value = 2.49 x 10(-3); corrected p-value = 0.03; FDR q-value = 0.06) were significantly associated with gastrointestinal toxicity after correction for multiple testing. Those patients who undergone previous prostatectomy were less prone to develop genitourinary toxicity (OR= 0.38; 95% CI: 0.18-0.71; uncorrected p-value =4.95 x 10(-3); corrected p-value = 0.03; FDR q-value = 0.08). Our study excludes the possibility of a >2-fold risk increase in genitourinary acute toxicity being due to rs1801516 ATM SNP, the rs1805386 and rs1805388 LIG4 markers, as well as all the SNPs evaluated in the ERCC2, MLH1 and XRCC3 genes. Conclusions: The XRCC3 rs1799794 SNP and the mean dose received by the rectum are associated with the development of gastrointestinal toxicity after 3D-CRT. (C) 2012 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 105 (2012) 321-328

Fichtenbaum, E. J., et al. (2012). "CK5, CK5/6, and Double-Stains CK7/CK5 and p53/CK5 Discriminate In Situ vs Invasive Urothelial Cancer in the Prostate." American Journal of Clinical Pathology 138(2): 190-197.

For primary bladder tumors, distinguishing urothelial carcinoma (UC) invading the fibromuscular stroma of the prostate (pT4a) from in situ UC involving prostatic ducts can be difficult. Immunohistochemical markers (cytokeratin [CK] 5/6, CK5, CK7, CK20, p53, p63, high-molecular-weight keratin [HMWK], androgen receptor, prostate-specific antigen [PSA], prostate specific acid phosphatase [PSAP], laminin, CD44s, CD141) were assessed for their usefulness in determining depth of UC invasion in the prostate. In cystoprostatectomy specimens containing in situ UC in prostatic ducts, both CK5/6 and CK5 clearly differentiated prostatic basal cells from in situ UC. The remaining markers were not effective in determining depth of tumor invasion. Double-stain combinations CK7/CK5 and p53/CK5 were performed and robustly color contrasted in situ tumor from surrounding basal cells. The use of CK5/6, CK5, CK7/CK5, or p53/CK5 is recommended to assist in determining the depth of UC invasion in the prostate when histologic findings are equivocal.

Fontenete, S., et al. (2012). "Molecular Study of the PCA3 Gene: Genotypic Analysis of PCA3 Polymorphism -845G > A and Metastatic Prostate Cancer." Genetic Testing and Molecular Biomarkers 16(5): 418-422.

Aims: The prostate cancer gene 3 (PCA3) is a prostate-specific, non-protein-coding RNA. It is overexpressed in prostate cancer compared with the normal prostate and has a negative expression in other tissues. This case-control study sought to analyze the frequency of the polymorphism PCA3 -845 G>A in participants without prostate cancer and patients with metastatic prostate cancer. Results: Carriers of GA and AA genotype had a higher risk for metastatic prostate cancer (odds ratio [OR] for genotype GA, 1.79 [95% confidence interval (CI), 1.14-2.29]; p = 0.007; OR for genotype AA, 2.38 [95% CI, 1.22-4.65]; p = 0.006). Furthermore, the recessive model showed that A allele carriers have an increased risk for developing metastatic prostate cancer (OR, 1.91 [95% CI, 1.26-2.90]; p = 0.001). Conclusions: These results suggest a link between PCA3 and metastatic prostate cancer. The evaluation of individual genetic profiles, according to the PCA3 -845 G > A polymorphism, may elucidate the function of this gene and the mechanisms involved in its regulation and role in prostate cancer.

Fowler, C. J., et al. (2013). "Tumour epithelial expression levels of endocannabinoid markers modulate the value of endoglin-positive vascular density as a prognostic marker in prostate cancer." Biochimica Et Biophysica Acta-Molecular and Cell Biology of Lipids 1831(10): 1579-1587.

Fatty acid amide hydrolase (FAAH) is responsible for the hydrolysis of the endogenous cannabinoid (CB) receptor ligand anandamide. Here we have investigated whether the expression levels of FAAH and CB1 receptors influence the prognostic value of markers of angiogenesis in prostate cancer. Data from a cohort of 419 patients who were diagnosed with prostate cancer at transurethral resection for lower urinary tract symptoms, of whom approximately 2/3 had been followed by expectancy, were used. Scores for the angiogenesis markers endoglin and von Willebrand factor (vWf), the endocannabinoid markers fatty acid amide hydrolase (FAAH) and cannabinoid CB1 receptors and the cell proliferation marker Ki-67 were available in the database. For the cases followed by expectancy, the prognostic value of endoglin was dependent upon the tumour epithelial FAAH immunoreactivity (FAAH-IR) and CB1IR scores, and the non-malignant epithelial FAAH-IR scores, but not the non-malignant CB1IR scores or the tumour blood vessel FAAH-IR scores. This dependency upon the tumour epithelial FAAH-IR or CB1IR scores was less apparent for vWf, and was not seen for Ki-67. Using an endoglin cut-off value of 10 positively stained vessels per core and a median split of tumour FAAH-IR, four groups could be generated, with 15 year of disease-specific survival (%) of 68 +/- 7 (low endoglin, low FAAH), 45 +/- 11 (high endoglin, low FAAH), 77 +/- 6 (low endoglin, high FAAH) and 21 +/- 10 (high endoglin, high FAAH). Thus, the cases with high endoglin and high FAAH scores have the poorest rate of disease-specific survival. At diagnosis, the number of cases with tumour stages 1a-1b relative to stages 2-4 was sensitive to the endoglin score in a manner dependent upon the tumour FAAH-IR. It is concluded that the prognostic value of endoglin as a marker of neovascularisation in prostate cancer can be influenced by the expression level of markers of the endocannabinoid system. This article is part of a Special Issue entitled Lipid Metabolism in Cancer. (C) 2012 Elsevier B.V. All rights reserved.

Fradet, Y. (2009). "Biomarkers in prostate cancer diagnosis and prognosis: beyond prostate-specific antigen." Current Opinion in Urology 19(3): 243-246.

Purpose of review To review the most recent advances in genetic testing for prostate cancer risk and of new molecular diagnostic assays to improve diagnostic accuracy and treatment decision beyond prostate-specific antigen (PSA) testing. Recent findings Multiple independent studies had demonstrated evidence that genetic variations in three regions of chromosome 8q24 and one each at 17q12 and 17q24.3 are independent predictors of prostate cancer risk in addition to family history and serum PSA levels. The small percentage of individuals with several anomalies can have up to 10 times the risk of prostate cancer. Novel molecular urine tests have been studied, and the prostate cancer antigen 3 RNA detection has been studied most extensively and is now commercially available. It provides an independent and synergistic information to predict a higher or lower risk of prostate cancer at given PSA level and can further help predict the tumor volume and Gleason grade found on the prostatectomy specimen. Sensitivity of the prostate cancer antigen 3 test could be improved by the detection of the fusion gene transcripts transmembrane protease serine 2-E26 transformation specific-related gene and serine peptidase inhibitor Kazal type 1 who may in addition allow the identification of prostate cancer patients at higher risk of life-threatening disease. Summary The challenge in the years to come will be to introduce these new gene-based diagnostic and prognostic tests in algorithms integrating the other known risk factors of age, ethnicity, family history and PSA level to better tailor diagnostic and therapeutic strategies.

Fujita, K., et al. (2009). "Endoglin (CD105) as a urinary and serum marker of prostate cancer." International Journal of Cancer 124(3): 664-669.

We have previously shown that endoglin (CD105) is upregulated in prostatic fluid of men with large volume prostate cancer. We chose to assess endoglin levels in urine and serum from men with prostate cancer or at increased risk for the disease: Urine samples were collected after digital rectal examination (DRE) from 99 men whose cancer status was confirmed by biopsy, and serum samples were collected from 20 men without prostate cancer at low risk for the disease and from 69 men diagnosed with prostate cancer that subsequently underwent radical prostatectomy (30 pT2, 39 pT3). Endoglin levels were assessed by ELISA. Urinary endoglin was elevated in men with biopsy-positive prostate cancer compared to biopsy-negative men (p = 0.0014). Urinary endoglin levels in men with prostate cancer correlated with radical prostatectomy tumor volume. The area under the receiver operating characteristic (ROC) curve was 0.72 for urinary endoglin and 0.50 for serum prostate-specific antigen (PSA; sensitivity for cancer detection 73%, specificity 63%). There were no differences in serum endoglin between normal and cancer cases, but there were increases in serum endoglin in non-organ confined (NOC, pT3+) versus organ-confined (OC, pT2) cases (p = 0.0004). The area under the ROC curve was 0.75 for serum endoglin and 0.63 for PSA for predicting NOC status, with a sensitivity of 67% and a specificity of 80%. In conclusion, elevations in post-DRE urinary endoglin suggest there may be value in further studying endoglin as a urinary biomarker of prostate cancer. Endoglin levels in both urine and serum may aid in prostate cancer detection and prognostication. (C) 2008 Wiley-Liss. Inc.

Fujita, K., et al. (2011). "Immunomodulatory IL-18 binding protein is produced by prostate cancer cells and its levels in urine and serum correlate with tumor status." International Journal of Cancer 129(2): 424-432.

Cytokines may play a role in the initiation and progression of prostate cancer. A cytokine antibody array was previously applied to prostatic fluid obtained from patients with prostate cancer, and interleukin 18 binding protein (IL-18BP), a potent inhibitor of interleukin 18, was noted to be significantly upregulated in cases with large volume disease. We sought to further characterize the association of IL-18BP with prostate cancer and determine whether IL-18BP levels in patient serum and urine samples had clinical relevance. IL-18BP was expressed and secreted by the prostate cancer cell lines DU145 and PC3 but not by LNCaP and CWR22, upon interferon-gamma (IFN-gamma) stimulation. IFN-gamma-induced secretion of IL-18BP was enhanced by added TNF-alpha, IFN-alpha and IFN-beta. The IL-18BP secreted from DU145 and PC3 functionally inhibited IL-18. Immunohistochemical analyses showed positive IL-18BP staining in prostate cancer cells as well as in macrophages in radical prostatectomy specimens. Significant differences in urinary IL-18BP levels (normalized by total protein) collected post-DRE were found between cases with and without cancer on biopsy (p = 0.02) and serum IL-18BP levels correlated with Gleason score (p = 0.03). Our finding of elevated IL-18BP secretion from prostate cancer cells suggests an attempt by cancer to escape immune surveillance. IL-18BP merits further study as a marker of aggressive prostate cancer and as a therapeutic target.

Fujita, K., et al. (2008). "Cytokine profiling of prostatic fluid from cancerous prostate glands identifies cytokines associated with extent of tumor and inflammation." Prostate 68(8): 872-882.

BACKGROUND. Cytokines are key mediators of inflammation that may relate to Prostate cancer initiation and progression, and that may be useful markers of prostatic neoplasia and related inflammation. In order to better understand the relationship between cytokines and prostate cancer, we profiled cytokines in prostatic fluids obtained from cancerous prostate glands and correlated them to both cancer status and inflammatory grade. METHODS. Prostatic fluid was collected from fresh radical prostatectomy specimens and analyzed by cytokine antibody microarray. For comparison, cases were selected from patients with either minimal or extensive cancer volume on final pathology. Among the cytokines with the greatest difference between the tumor volume groups, eight had their levels quantitated by ELISA. In addition, the grade of prostatic inflammation by neutrophils, macrophages and lymphocytes was scored for each case and examined for correlations with cytokine levels. RESULTS. Among 174 cytokines analyzed, HGF was the most increased (6.57-fold), and along with IL18Bpa was significantly elevated in patients with extensive disease compared to those with minimal disease. IL17, GITR, and ICAM-1 were elevated in specimens with significant neutrophilic inflammation into gland lumina, and IL1813pa, 11,17, GITR, and ICAM-1 were elevated in specimens with significant lymphocytic inflammation in prostatic stroma. CONCLUSIONS. Prostatic fluid cytokines were identified that may be useful for early cancer detection and prognostication efforts and for assessment of prostatic inflammation, particularly if they can be found not only in prostatic fluids obtained ex vivo, but in expressed prostatic secretions or urine samples from men with prostates still in situ.

Fujita, K., et al. (2011). "Prostatic Inflammation Detected in Initial Biopsy Specimens and Urinary Pyuria are Predictors of Negative Repeat Prostate Biopsy." Journal of Urology 185(5): 1722-1727.

Purpose: Asymptomatic prostatic inflammation may cause increased prostate specific antigen in some men, leading to unnecessary repeat prostate biopsy. We determined whether histological findings of inflammation in initial biopsy specimens and/or clinical indicators of inflammation could predict the outcome of subsequent biopsy in men with a negative initial biopsy. Materials and Methods: A total of 105 Japanese men with increased prostate specific antigen underwent repeat prostate biopsy after initial biopsy revealed no evidence of carcinoma. Of the cases 45 (42.8%) were positive for prostate cancer at repeat biopsy. We evaluated initial biopsy specimens for evidence of inflammation by mononuclear and polymorphonuclear leukocytes, serum and urinary white blood count, and C-reactive protein. Results: Polymorphonuclear leukocyte infiltrates, urinary white blood count, patient age, prostate specific antigen at repeat biopsy, prostate volume, prostate specific antigen velocity and prostate specific antigen density were associated with the repeat biopsy outcome (p < 0.05). Multivariate analysis revealed that age, prostate specific antigen density and urinary white blood count were independent predictors of outcome. On subgroup analysis of 63 men with serum prostate specific antigen less than 10 ng/ml before initial biopsy polymorphonuclear and mononuclear leukocyte inflammation, age, prostate specific antigen at repeat biopsy, prostate volume, prostate specific antigen velocity and prostate specific antigen density were associated with the outcome of repeat biopsy (p < 0.05). Multivariate analysis showed that polymorphonuclear leukocyte infiltrate, prostate specific antigen density and age were independent predictors. Conclusions: Age, prostate specific antigen density, polymorphonuclear leukocyte inflammation in initial biopsy specimens and urinary pyuria are indicators of benign repeat biopsy. They help avoid unnecessary repeat biopsy in men with increased prostate specific antigen.

Gakis, G., et al. (2013). "Do we use the right criteria for determining the clinical significance of incidental prostate cancer at radical cystoprostatectomy?" Scandinavian Journal of Urology 47(5): 358-362.

Prostate-sparing techniques have been advocated to improved functional outcomes after radical cystoprostatectomy (RCP) for invasive bladder cancer, but this may endanger the oncological outcome. This review addresses the current status of risk factors of prostate cancer (PCa) recurrence in patients with incidental PCa after RCP. The overall 7-year risk of PCa recurrence after RCP is approximately 9%. Increased risk has been suggested in the presence of clinically significant PCa as: >= pT3a stage, presence of lymph-node metastasis, positive surgical margins, Gleason pattern >= 4, tumour multifocality (three or more foci) and tumour volume >0.5 cm(3). However, the prognostic significance of these parameters has not been evaluated within multivariable analyses so far. Preoperatively elevated prostate-specific antigen (PSA) values correlate weakly with the clinical significance of incidental PCa, while prostate biopsy has a limited accuracy for detecting incidental PCa in the preoperative setting. Genetic markers, e.g. the prostate stem cell antigen (PSCA) gene, have recently been associated with risk of recurrence in patients with incidental PCa. Incidental PCa at RCP is usually clinically insignificant. Yet, clinicopathological parameters for clinical significant cancers have not been investigated independently in the literature so far. Consequently, lifelong PSA surveillance should be conducted in all patients with incidental PCa after RCP. In the presence of clinically significant PCa treatment decisions should be based not only on histological criteria but also on patient-centred parameters (e.g. patient age and comorbidities). Assessment of PSCA expression in RCP specimens may enable improved risk assessment for PCa recurrence after RCP.

Gao, L., et al. (2010). "Tissue kallikrein promotes prostate cancer cell migration and invasion via a protease-activated receptor-1-dependent signaling pathway." Biological Chemistry 391(7): 803-812.

We recently demonstrated that tissue kallikrein (TK) promotes keratinocyte migration through activation of protease-activated receptor-1 (PAR(1)) and transactivation of the epidermal growth factor receptor (EGFR). In this study, we investigated the potential role of PAR, in mediating the effect of TK on cancer cell migration, invasion and proliferation. Our results show that TK promotes DU145 prostate cancer cell migration in a concentration-dependent manner, but has no effect on A549 lung cancer cells. Active TK markedly increases DU145 cell migration and invasion, which are blocked by aprotinin but minimally affected by icatibant; kinin treatment has little effect. TK-induced cell migration and invasion are abolished by inhibition of PAR, using a pharmacological inhibitor or RNA interference. The effect of TK on cell migration and invasion are also blocked by inhibitors of protein kinase C, c-Src, matrix metalloproteinase, EGER and extracellular signal-regulated kinase (ERK). Moreover, TK stimulates ERK phosphorylation, which is inhibited by an EGER antagonist. Additionally, TK but not kinin stimulates DU145 cell proliferation through activation of the kinin B2 receptor, but not PAR, and EGFR. These results indicate differential signaling pathways mediated by TK in promoting prostate cancer cell migration and invasion via PAR, activation, and proliferation via kinin B2 receptor stimulation.

Geisler, C., et al. (2015). "Identification and validation of potential new biomarkers for prostate cancer diagnosis and prognosis using 2D-DIGE and MS." BioMed research international 2015: 454256-454256.

This study was designed to identify and validate potential new biomarkers for prostate cancer and to distinguish patients with and without biochemical relapse. Prostate tissue samples analyzed by 2D-DIGE (two-dimensional difference in gel electrophoresis) and mass spectrometry (MS) revealed downregulation of secernin-1 (P<0.044) in prostate cancer, while vinculin showed significant upregulation (P<0.001). Secernin-1 overexpression in prostate tissue was validated using Western blot and immunohistochemistry while vinculin expression was validated using immunohistochemistry. These findings indicate that secernin-1 and vinculin are potential new tissue biomarkers for prostate cancer diagnosis and prognosis, respectively. For validation, protein levels in urine were also examined by Western blot analysis. Urinary vinculin levels in prostate cancer patients were significantly higher than in urine from nontumor patients (P=0.006). Using multiple reaction monitoring-MS (MRM-MS) analysis, prostatic acid phosphatase (PAP) showed significant higher levels in the urine of prostate cancer patients compared to controls (P=0.012), while galectin-3 showed significant lower levels in the urine of prostate cancer patients with biochemical relapse, compared to those without relapse (P=0.017). Three proteins were successfully differentiated between patients with and without prostate cancer and patients with and without relapse by using MRM. Thus, this technique shows promise for implementation as a noninvasive clinical diagnostic technique.

Geisler, C., et al. (2015). "Identification and Validation of Potential New Biomarkers for Prostate Cancer Diagnosis and Prognosis Using 2D-DIGE and MS." BioMed research international.

Girard, F. P., et al. (2010). "Detecting soluble Clusterin in in-vitro and in-vivo models of prostate cancer." Neoplasma 57(5): 488-493.
PSA, the only relevant marker for prostate cancer, has a low predictive value; moreover its low threshold leads to unnecessary biopsies with associated complications. Identification of prognostic factors is an important goal in prostate cancer. In the search for new markers, clusterin, has some potential as it is closely linked with cancer progression and resistance to apoptosis. We looked at the expression of secreted clusterin (sCLU) in prostate cells to determine correlations with progression and drug resistance. The plasmatic expression of sCLU was also investigated in order to use it as a potential marker for prostate cancer. sCLU expression was studied using Western blotting on cultured prostate cells, PWR-1E, PC3 and PC3 Docetaxel resistant cells in the cytosol and culture medium. An inhouse ELISA test was developed to determine sCLU expression in culture media and plasma samples. A patient cohort was identified from the Prostate Cancer Research Consortium Bio-Resource and plasmatic expression of sCLU was studied using western blotting and the inhouse ELISA test. Only the fully processed form of sCLU was identified in the medium of cells with increased expression associated with increased progression of disease and resistance to docetaxel. Plasmatic expression of sCLU was significantly higher in the plasma of patients with high grade prostate cancer with extracapsular extension than in the plasma of prostate cancer patients without extracapsular extension. Plasmatic sCLU may be an effective prognostic marker of prostate cancer and needs to be tested in a multimarker approach.

Goo, Y. A. and D. R. Goodlett (2010). "Advances in proteomic prostate cancer biomarker discovery." Journal of Proteomics 73(10): 1839-1850.

Prostate cancer is the most common non-cutaneous cancer in men in the United States. For reasons largely unknown, the incidence of prostate cancer has increased in the last two decades, in spite or perhaps because of a concomitant increase in serum prostate-specific antigen (PSA) screening. While PSA is acknowledged not to be an ideal biomarker for prostate cancer detection, it is however widely used by physicians due to lack of an alternative. Thus, the identification of a biomarker(s) that can complement or replace PSA represents a major goal for prostate cancer research. Screening complex biological specimens such as blood, urine, and tissue to identify protein biomarkers has become increasingly popular over the last decade thanks to advances in proteomic discovery methods. The completion of human genome sequence together with new development in mass spectrometry instrumentation and bioinformatics has been a major driving force in biomarker discovery research. Here we review the current state of proteomic applications as applied to various sample sources including blood, urine, tissue, and "secretome" for the purpose of prostate cancer biomarker discovery. Additionally, we review recent developments in validation of putative markers, efforts at systems biology approach, and current challenges of proteomics in biomarker discovery. (C) 2010 Published by Elsevier B.V.

Goo, Y. A., et al. (2009). "Identification of Secreted Glycoproteins of Human Prostate and Bladder Stromal Cells by Comparative Quantitative Proteomics." Prostate 69(1): 49-61.

BACKGROUND. Functional development of the prostate is governed by stromal mesenchyme induction and epithelial response. Stromal/epithelial signaling can be mediated through direct cell-cell contact and diffusible factors and their cell surface receptors. These inducers are likely secreted or membrane-associated extracellular proteins. Given the importance of intercellular communication, it is possible that diseases like cancer could arise from a loss of this communication. One approach to gain a molecular understanding of stromal cells is to identify, as a first step, secreted stromal signaling factors. We proposed to do this by comparative analysis between bladder and prostate. METHODS. Secreted proteins were identified from cultured normal prostate and bladder stromal mesenchyme cells by glycopeptide-capture method followed by mass spectrometry. Differences in protein abundance between prostate and bladder were quantified from calculated peptide ion current area (PICA) followed by Western validation. Functional and pathway analyses of the proteins were carried out by Gene Ontology (GO) and Teranode software. RESULTS. This analysis produced a list of 116 prostate and 84 bladder secreted glycoproteins with ProteinProphet probability scores >= 0.9. Stromal proteins upregulated in the prostate include cathepsin L, follistatin-related protein, neuroendocrine convertase, tumor necrosis factor receptor, and others that are known to be involved in signal transduction, extracellular matrix interaction, differentiation and transport. CONCLUSIONS. We have identified a number of potential proteins for stromal signaling and bladder or prostate differentiation program. The prostate stromal/epithelial signaling may be accomplished through activation of the ECM-receptor interaction, complement and coagulation cascades, focal adhesion and cell adhesion pathways. Prostate 69: 49-61, 2009. (C) 2008 Wiley-Liss, Inc.

Gooch, J., et al. (2014). "Application of fluorescent substrates to the in situ detection of prostate specific antigen." Talanta 125: 210-214.

The forensic identification of body fluids frequently presents an important source of genetic material and investigative interpretation. However, presumptive testing techniques presently employed in the discrimination of biological fluids are subject to criticism for poor specificity, lack of fluid localisation ability and detrimental effects on DNA recovery rates. The recognition of fluid-specific biomarkers by fluorogenic substrates may provide a novel resolution to these issues but research has yet to establish any pertinent in situ fluid detection applicability. This study therefore utilises a fluorogenic substrate (Mu-HSSKLQ-AFC) specific to the seminal protein prostate specific antigen in an effort to detect human semen deposited on a number of surfaces typical to criminal investigation. The ability of fluorescent fluorogenic substrates to simultaneously identify and visualise biological fluids in situ is demonstrated for the first time, whilst the production of complete SIR profiles from fluid sources is also confirmed to be completely unaffected by substrate application. (C) 2014 Elsevier B.V. All rights reserved.

Grainger, E. M., et al. (2008). "A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen." Nutrition and Cancer-an International Journal 60(2): 145-154.

Tomato and soy products are hypothesized to reduce the risk of prostate cancer or enhance efficacy of therapy. A study was completed to determine if men with active prostate cancer will adhere to a dietary intervention rich in tomato products and a soy protein supplement men (n = 41) with recurrent, asymptomatic prostate cancer were randomized among 2 groups: Group A (n = 20) consumed tomato products (no soy) for Weeks 0 through 4, targeting a minimum of 25 mg of lycopene/day. Group B (n = 21) consumed soy (no tomatoes) for Weeks 0 through 4, providing 40 g of soy protein/day. For Weeks 4 through 8, all men consumed a combined tomato-rich diet and soy supplements. No grade II through IV toxicities were observed. During Weeks 0 through 4, mean daily lycopene intake for Group A was 43 mg (15 mg) and mean soy intake for Group B was 39 g (1 g), remaining similar during Weeks 4 through 8. Serum lycopene increased from 0.72 +/- 0.09 mu mol/l to 1.21 +/- 0.10 mu mol/l (P < 0.0001) and urinary isoflavone excretion increased from not detectable to 54.1 +/- 5.7 mu mol/l (P < 0.05) with 8 wk of diet intervention. Serum prostate-specific antigen decreased between Weeks 0 and 8 for 14/41 men (34%). Mean serum vascular endothelial growth factor for the entire group was reduced from 87 to 51 ng/ml (P < 0.05) over 8 wk. In conclusion, prostate cancer patients will consume diets rich in tomato products and soy with excellent compliance and bioavailability of phytochemicals. Further studies combining tomato and soy foods to determine efficacy for prostate cancer prevention or management are encouraged.

Groot, M. J. (2006). "Effects of phyto-oestrogens on veal calf prostate histology." Veterinary Research Communications 30(6): 587-598.

In veal calf production plant-based proteins are frequently included in milk replacer fed to the animals. Since soy products, which are mostly used, are known for their high levels of phyto-oestrogens, the effects of these feeds on the veal calf prostate were examined. Goal was to determine whether these compounds could interfere with histological screening for oestrogenic growth promoters. In a feeding experiment, four groups of veal calves fed plant-based protein-supplemented milk replacer (PBM), containing 5% soy concentrate, 5% soy isolate, 5% wheat gluten and 2% potato protein, for 4 weeks were compared to animals fed dairy-based control feed (DBM); animals treated with estradiol benzoate, diethylstilbestrol and ethinylestradiol served as positive controls. Daidzein and genistein levels measured in feed and urine showed high levels of genistein and daidzein in the soy isolate and soy concentrate supplemented feeds. Genistein and daidzein were also found in the urine of the animals that were fed these feeds. Haematoxylin-eosin-stained prostate sections of PBM-fed animals showed slight hyperplasia and some dilated tubules as compared to the DBM-fed group, but no metaplasia, which is used for screening for oestrogenic hormones. The positive controls showed extensive squamous metaplasia. Immunohistochemical staining for cytokeratin 5 (using RCK 103 monoclonal antibody) in basal cells showed a normal staining pattern of basal cells in the DBM-fed calves and extensive basal cell proliferation and squamous metaplasia in the oestrogen-treated positive control animals. PBM-fed calves showed no increase of basal cell staining but showed elongations of the basal cells in most animals, sometimes resulting in circular figures. It is concluded that the feeds examined in this study did not interfere with histological screening for oestrogens in male veal calves.

Guo, X.-Q., et al. (2011). "The progress of TMPRSS2-ETS gene fusions and their mechanism in prostate cancer." Yi chuan = Hereditas / Zhongguo yi chuan xue hui bian ji 33(2): 117-122.

The gene fusions between transmembrane protease serine 2 (TMPRSS2) and E26 (ETS) transcription factors are present in over 50% of patients with prostate cancer. TMPRSS2-ERG is the most common gene fusion type. The ERG overexpression induced by TMPRSS2-ERG gene fusion contributes to the development of prostate cancer. Both androgen receptor binding and genotoxic stress induce chromosomal proximity and TMPRSS2-ETS gene fusions. TMPRSS2-ERG gene fusion functions as a biomarker for prostate cancer, which can be easily detected in urine. This review focuses on the characteristics, oncogenic and rearranged mechanism, and clinical application of TMPRSS2-ETS gene fusions.

Gurbuz, C., et al. (2011). "Reducing Infectious Complications after Transrectal Prostate Needle Biopsy Using a Disposable Needle Guide: Is It Possible?" International Braz J Urol 37(1): 79-84.

Purpose: To investigate whether the use of a disposable needle guide results in a decreased incidence of infectious complication after transrectal prostate needle biopsy (TPNB). Materials and Methods: Fifty five patients who underwent 10-core TPNB were randomized into two groups. A pre-biopsy blood and, urine examination was performed in both groups. Group 1 (25 patients) underwent biopsy with disposable biopsy needle guide and Group 2 (30 patients) underwent biopsy with reusable biopsy needle guide. All patients had a blood and negative urine culture before the procedure. The patients received ciprofloxacin 500 mg twice a day beginning the day before the biopsy and continued for 3 days after. Serum C-reactive protein levels and urine and blood specimens were obtained 48h after the biopsy. Primary endpoint of the study was to determine the effect of needle guide on the bacteriologic urinary tract infection (UT) rate and secondary end point was to determine symptomatic UTI. Results: The mean age of the patients was 63.46 (range 55 to 68) years. There were no significant differences regarding the prostate-specific antigen level, prostate size, existence of comorbidity in two groups before the procedure. Bacteriologic and symptomatic UTI was detected in 4% vs. 6.6% and 4% vs. 3.9% in Group 1 and 2 relatively (P>0.05). Conclusion: The use of a disposable needle guide does not appear to minimize infection risk after TPNB. Large scale and randomized studies are necessary to determine the effect of disposable needle guide on infection rate after TPNB.

Haj-Ahmad, T. A., et al. (2014). "Potential Urinary Protein Biomarker Candidates for the Accurate Detection of Prostate Cancer among Benign Prostatic Hyperplasia Patients." Journal of Cancer 5(2): 103-114.

Globally, Prostate cancer (PCa) is the most frequently occurring non-cutaneous cancer, and is the second highest cause of cancer mortality in men. Serum prostate specific antigen (PSA) has been the standard in PCa screening since its approval by the American Food & Drug Administration (FDA) in 1994. Currently, PSA is used as an indicator for PCa - patients with a serum PSA level above 4ng/mL will often undergo prostate biopsy to confirm cancer. Unfortunately fewer than similar to 30% of these men will biopsy positive for cancer, meaning that the majority of men undergo invasive biopsy with little benefit. Despite PSA's notoriously poor specificity (33%), there is still a significant lack of credible alternatives. Therefore an ideal biomarker that can specifically detect PCa at an early stage is urgently required. The aim of this study was to investigate the potential of using deregulation of urinary proteins in order to detect Prostate Cancer (PCa) among Benign Prostatic Hyperplasia (BPH). To identify the protein signatures specific for PCa, protein expression profiling of 8 PCa patients, 12 BPH patients and 10 healthy males was carried out using LC-MS/MS. This was followed by validating relative expression levels of proteins present in urine among all the patients using quantitative real time-PCR. This was followed by validating relative expression levels of proteins present in urine among all the patients using quantitative real time-PCR. This approach revealed that significant the down-regulation of Fibronectin and TP53INP2 was a characteristic event among PCa patients. Fibronectin mRNA down-regulation, was identified as offering improved specificity (50%) over PSA, albeit with a slightly lower although still acceptable sensitivity (75%) for detecting PCa. As for TP53INP2 on the other hand, its down-regulation was moderately sensitive (75%), identifying many patients with PCa, but was entirely non-specific (7%), designating many of the benign samples as malignant and being unable to accurately identify more than one negative.

Hamelin-Peyron, C., et al. (2014). "Prostate cancer biomarker annexin A3 detected in urines obtained following digital rectal examination presents antigenic variability." Clinical Biochemistry 47(10-11): 901-908.

Objectives: Annexin A3 (ANXA3) is a potential marker for prostate cancer (PCa). We aimed to develop robust immunoassays suitable for quantifying ANXA3 in urine samples obtained following digital rectal examination (DRE) in order to facilitate the diagnostic performance evaluation of this marker. Design and methods: Anti-ANXA3 monoclonal antibodies were generated and their epitopes mapped. Two different ANXA3 assay prototypes were established on the VIDAS (R) automated immunoanalyser and analytical validation was carried out using post-DRE urine samples obtained from patients with PCa (n = 23) or benign prostate hyperplasia (n = 31). Results: The assays had the same capture antibody (TGC44) but different detection antibodies (13A12 or 5C5), recognizing novel distinct epitopes. Both had a lower limit of quantification <1 ng/mL and were highly specific for ANXA3, not cross-reacting with other annexins. Interassay imprecision was <= 11% and <= 15% for 13A12 and 5C5 assays, respectively. Surprisingly, a total lack of correlation was observed between ANXA3 levels measured by these two assays in post-DRE urines, indicating detection of distinct antigenic variants. Two freeze-thaw cycles did not affect analyte stability in either assay, whereas a lack of stability of antigenic variants was observed when samples were stored at -80 degrees C for 1 month. Conclusions: Two different antigenic variants of ANXA3 are present in post-DRE urines and their clinical significance for diagnosis of prostate cancer should be further investigated. These variants are not stable over time in samples preserved at -80 degrees C. Until this issue is resolved, ANXA3 should only be measured in freshly collected samples. (C) 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Hamilton-Reeves, J. M., et al. (2007). "Soy protein isolate increases urinary Estrogens and the ratio of 2 : 16 alpha-hydroxyestrone in men at high risk of prostate cancer." Journal of Nutrition 137(10): 2258-2263.

Specific estrogen metabolites may initiate and promote hormone-related cancers. In epidemiological studies, significantly lower excretion of urinary estradiol (E2) and lower ratio of urinary 2-hydroxy estrogens to 16 alpha-hydroxyestrone (2:16 OH-E1) have been reported in prostate cancer cases compared to controls. Although soy supplementation has been shown to increase the ratio 2:16 OH-E1 in women, no studies to our knowledge have investigated the effects of soy supplementation on estrogen metabolism in men. The objective of this randomized controlled trial was to determine the effects of soy protein isolate consumption on estrogen metabolism in men at high risk for developing advanced prostate cancer. Fifty-eight men supplemented their habitual diets with I of 3 protein isolates: 1) isoflavone-rich soy protein isolate (SPI+) (107 mg isoflavones/d); 2) alcohol-washed soy protein isolate SPI-) (<6 mg isoflavones/d); or 3) milk protein isolate (MPI), each providing 40 g protein/d. At 0, 3, and 6 mo of supplementation, the urinary estrogen metabolite profile was measured by GC-MS. Both soy groups had higher E2 excretion than the MPI group at 3 and 6 mo. After 6 mo of supplementation, the SPI+ group had a significantly higher urinary 2:16 OH-E1 ratio than the MPI group, Increased urinary E2 excretion and 2:16 OH-E1 ratio in men consuming soy protein isolate are consistent with studies in postmenopausal women and suggest that soy consumption may be beneficial in men at high risk of progressing to advanced prostate cancer as a result of effects on endogenous estrogen metabolism.

Hammarsten, P., et al. (2012). "Phospho-Akt Immunoreactivity in Prostate Cancer: Relationship to Disease Severity and Outcome, Ki67 and Phosphorylated EGFR Expression." PloS one 7(10).

Background: In the present study, we have investigated the prognostic usefulness of phosphorylated Akt immunoreactivity (pAkt-IR) in prostate cancer using a well-characterised tissue microarray from men who had undergone transurethral resection due to lower urinary tract symptoms. Methodology/Principal Findings: pAkt-IR in prostate epithelial and tumour cells was assessed using a monoclonal anti-pAkt (Ser(473)) antibody. Immunoreactive intensity was determined for 282 (tumour) and 240 (non-mlignant tissue) cases. Tumour pAkt-IR scores correlated with Gleason score, tumour Ki67-IR (a marker of cell proliferation) and tumour phosphorylated epidermal growth factor receptor (pEGFR)-IR. For cases followed with expectancy, a high tumour pAkt-IR was associated with a poor disease-specific survival, and the prognostic information provided by this biomarker was additive to that provided by either (but not both) tumour pEFGR-IR or Ki67-IR. Upon division of the cases with respect to their Gleason scores, the prognostic value of pAkt-IR was seen for patients with Gleason score 8-10, but not for patients with Gleason score 6-7. Conclusions/Significance: Tumour pAkt-IR is associated with both disease severity and disease-specific survival. However, its clinical use as a biomarker is limited, since it does not provide prognostic information in patients with Gleason scores 6-7.

Hansen, J., et al. (2013). "Assays for Prostate Cancer Changing the Screening Paradigm?" Molecular Diagnosis & Therapy 17(1): 1-8.

Prostate cancer (PCa) screening and detection have changed dramatically since the introduction of serum prostate-specific antigen (PSA) testing. Despite the resulting improvement in early PCa detection and stage migration, in clinical practice the use of PSA testing may cause overdetection and ultimately overtreatment. As a consequence, novel biomarkers are needed to increase the specificity of PCa detection. The aim of this article is to present an overview of novel blood- and urine-based biomarkers that may optimize PCa detection, with improved identification of patients with significant PCa and avoidance of unnecessary prostate biopsies. A systematic and comprehensive PubMed search was performed using the MeSH search terms 'prostate cancer', 'biomarker', 'marker', and 'detection'. Results were restricted to the English language. Several blood- and urine-based biomarkers have the potential to improve prediction of the presence and/or significance of PCa. Ideally, biomarkers should be used in combination within multivariate models, leading to superior accuracy for prediction of any PCa or clinically significant PCa, compared with the use of a single marker.

Hayashi, T., et al. (2009). "Immunohistochemical analysis of Reg IV in urogenital organs: Frequent expression of Reg IV in prostate cancer and potential utility as serum tumor marker." Oncology Reports 21(1): 95-100.

Regenerating islet-derived family, member 4 (Reg IV) is a candidate marker for cancer and inflammatory bowel disease and is associated with neuroendocrine and intestinal differentiation. We have reported that 14% of prostate cancer (PCa) cases are positive for Reg IV by immunohistochemistry. In the present Study, We performed immunohistochemical analysis of Reg IV in other major urological cancers, including 101 renal cell carcinoma (RCC), and 95 urothelial carcinoma (UC) of urinary bladder by immunohistochemistry. We also investigated neuroendocrine differentiation by chromogranin A and synaptophysin staining along with intestinal differentiation by MUC2 staining. Immunohistochemical analysis of Reg IV revealed no expression of Reg IV in RCC, and only one case (1%) of UC expressed Reg IV. Neither neuroendocrine nor intestinal differentiation was found in RCC. Among 95 UC cases, neuroendocrine differentiation was detected in 13 cases (14%), and intestinal differentiation was observed in 33 cases (35%). In one Reg IV-positive UC case, MUC2 staining was observed. Since Reg IV expression was frequently found in PCa, we also measured Reg IV levels in sera from patients with PCa by enzyme-linked immuno-sorbent assay. The serum Reg IV concentration in PCa patients (n=38, mean +/- SE, 1.69 +/- 0.16 ng/ml) was significantly higher than that in control individuals (n=40, 1.28 +/- 0.11 ng/ml, P=0.0199, Mann-Whitney U test). The sensitivity and specificity for detection of PCa were 34% (13/38) and 90% (36/40), respectively. These results suggest that among major urologic cancers, Reg IV is expressed frequently in PCa, and that serum Reg IV represents a novel biomarker for PCa.

He, J., et al. (2015). "Analytical platform evaluation for quantification of ERG in prostate cancer using protein and mRNA detection methods." Journal of Translational Medicine 13.

Background: The established methods for detecting prostate cancer (CaP) are based on tests using PSA (blood), PCA3 (urine), and AMACR (tissue) as biomarkers in patient samples. The demonstration of ERG oncoprotein overexpression due to gene fusion in CaP has thus provided ERG as an additional biomarker. Based on this, we hypothesized that ERG protein quantification methods can be of use in the diagnosis of prostate cancer. Methods: An antibody-free assay for ERG3 protein detection was developed based on PRISM (high-pressure high-resolution separations with intelligent selection and multiplexing)-SRM (selected reaction monitoring) mass spectrometry. We utilized TMPRSS2-ERG positive VCaP and TMPRSS2-ERG negative LNCaP cells to simulate three different sample types (cells, tissue, and post-DRE urine sediment). Enzyme-linked immunosorbent assay (ELISA), western blot, NanoString, and qRT-PCR were also used in the analysis of these samples. Results: Recombinant ERG3 protein spiked into LNCaP cell lysates could be detected at levels as low as 20 pg by PRISM-SRM analysis. The sensitivity of the PRISM-SRM assay was approximately 10,000 VCaP cells in a mixed cell population model of VCaP and LNCaP cells. Interestingly, ERG protein could be detected in as few as 600 VCaP cells spiked into female urine. The sensitivity of the in-house ELISA was similar to the PRISM-SRM assay, with detection of 30 pg of purified recombinant ERG3 protein and 10,000 VCaP cells. On the other hand, qRT-PCR exhibited a higher sensitivity, as TMPRSS2-ERG transcripts were detected in as few as 100 VCaP cells, in comparison to NanoString methodologies which detected ERG from 10,000 cells. Conclusions: Based on this data, we propose that the detection of both ERG transcriptional products with RNA-based assays, as well as protein products of ERG using PRISM-SRM assays, may be of clinical value in developing diagnostic and prognostic assays for prostate cancer given their sensitivity, specificity, and reproducibility.

He, J., et al. (2015). "Analytical platform evaluation for quantification of ERG in prostate cancer using protein and mRNA detection methods." Journal of Translational Medicine 13: 418-418.

Hennenberg, M., et al. (2013). "Noradrenaline induces binding of Clathrin light chain A to alpha 1-adrenoceptors in the human prostate." Prostate 73(7): 715-723.

BACKGROUND Binding of clathrins or caveolin to G protein-coupled receptors may induce post-translational modifications of receptor function. Receptor regulation by clathrin requires cofactors ADP-ribosylation factor 6 (ARF6) and adaptin, while dynamin is required for clathrin- and caveolin-dependent mechanisms. OBJECTIVE To investigate the expression and 1-adrenoceptor binding of clathrins, caveolin, and their cofactors in the human prostate. METHODS Prostate tissue was obtained from radical prostatectomy. Expression of clathrin heavy chain (HC), clathrin light chain A and B (LCA, LCB), caveolin-1, ARF6, -adaptin, and dynamin-2 was studied by RT-PCR, Western blot, immunohistochemistry, and fluorescence staining. Interaction of 1A-adrenoceptors with clathrins and caveolin-1 was studied by coimmunoprecipitation. RESULTS mRNA and protein expression of clathrin HC, LCA, LCB, caveolin-1, dynamin-2, and -adaptin was detected in prostate tissues of each patient. Immunohistochemistry demonstrated the expression of clathrin HC, LCA, LCB, caveolin, dynamin, and -adaptin in stromal cells. Immunoreactivity for these proteins colocalized with -smooth muscle actin and 1A-adrenoceptors in double fluorescence staining. Coimmunoprecipitation demonstrated that 1A-adrenoceptors in prostate tissue interact with clathrin HC and LCB under resting conditions, but not with caveolin-1. Stimulation of prostate tissues with noradrenaline (30 mu M) in vitro induced binding of clathrin LCA to 1A-adrenoceptors. CONCLUSIONS The prostatic 1-adrenoceptor population is at least partially bound to clathrin HC and LCB. Upon receptor activation, prostate 1A-adrenoceptors bind clathrin LCA. This points to a new concept of post-translational 1-adrenoceptor regulation in the prostate, which includes receptor interaction with accessory binding partners. Prostate 73: 715723, 2013. (c) 2013 Wiley Periodicals, Inc.

Hennenberg, M., et al. (2011). "Beta-arrestin-2 is expressed in human prostate smooth muscle and a binding partner of alpha 1A-adrenoceptors." World Journal of Urology 29(2): 157-163.
Alpha1A-adrenoceptors are important regulators of prostatic smooth muscle tone and an important target for therapy of lower urinary tract symptoms. The function of heptahelical transmembrane receptors such as adrenoceptors can be regulated by beta-arrestin-2, which may bind to receptors besides G proteins. Here, we investigated the expression and alpha 1A-adrenoceptor binding of beta-arrestin-2 in the human prostate. Human prostatic tissues were obtained from patients undergoing radical prostatectomies. The expression of beta-arrestin-2 and alpha 1A-adrenoceptors was studied by RT-PCR, Western blot analysis, and immunohistochemistry. The protein-protein interaction between alpha 1A-adrenoceptors and beta-arrestin-2 was investigated by coimmunoprecipitation. RT-PCR and Western blot analysis demonstrated the expression of beta-arrestin-2 mRNA and protein in the human prostate. Immunohistochemistry demonstrated beta-arrestin-2 expression in smooth muscle and stromal cells. Coimmunoprecipitation studies demonstrated that alpha 1A-adrenoceptors in the human prostate may interact with beta-arrestin-2. Thus, specific binding of beta-arrestin-2 to alpha 1A-adrenoceptors was significantly higher than background during alpha 1A-adrenoceptor detection in beta-arrestin-2 precipitates (P < 0.001) or during beta-arrestin-2 detection in alpha 1A-adrenoceptor precipitates (P < 0.005). This interaction may be located to prostate smooth muscle cells, as expression of the alpha 1A-adrenoceptor was exclusively found in smooth muscle cells after immunohistochemical staining. With beta-arrestin-2, we identified a new binding partner of the alpha 1A-adrenoceptor in human prostate smooth muscle. Binding of beta-arrestin-2 may be involved in posttranslational regulation of prostate alpha 1A-adrenoceptors.

Hennenberg, M., et al. (2015). "Cooperative effects of EGF, FGF, and TGF-beta 1 in prostate stromal cells are different from responses to single growth factors." Life Sciences 123: 18-24.

Aims: Stromal growth is critical for prostate enlargement during benign prostatic hyperplasia (BPH). While responses of prostate cells to single growth factors have been well characterized, responses to multiple growth factors at once are poorly understood. Here, we examined the effects of combinations between epidermal growth factor (EGF), fibroblast growth factor (FGF), and transforming growth factor-beta 1 (TGF-beta 1) in human prostate stromal cells. Main methods: EGF, FGF, and TGF-beta 1 were applied to WPMY-1 cells, an immortalized, non-malignant line of stromal cells from the human prostate. Hypertrophic responses were assessed by protein/DNA ratio, and cyclin D1 mRNA by RT-PCR. Expression of EGF, FGF, and TGF-beta 1 and their receptors in human prostate tissue was analyzed by RT-PCR, Western blot, and fluorescence staining. Key findings: Hypertrophic responses to single growth factors and combinations were similar. Combinations showed additive effects on cyclin D1 mRNA. Combination of EGF with TGF-beta 1, but not EGF or TGF-beta 1 alone, caused assembly of cells to a new two-dimensional structure, being characterized by dense aggregates connected by branches of few cells. EGF and TGF-beta 1 were detected together in human prostates. Receptors for EGF and TGF-beta colocalized on stromal cells in human prostates. Significance: Responses of prostate stromal cells to combinations of EGF, FGF, and TGF-beta 1 may be quantitatively different, qualitatively different, or similar to responses to single growth factors. The combination of EGF and TGF-beta 1, but not EGF or TGF-beta 1 alone, induces aggregation of prostate stromal cells, which may be relevant for morphogenesis. (C) 2014 Elsevier Inc. All rights reserved.

Hennenberg, M., et al. (2013). "The cAMP effector EPAC activates Elk1 transcription factor in prostate smooth muscle, and is a minor regulator of alpha 1-adrenergic contraction." Journal of Biomedical Science 20.

Background: Prostate smooth muscle tone is regulated by alpha 1-adrenoceptor-induced contraction and cAMP-mediated relaxation. EPAC is an effector of cAMP, being involved in smooth muscle relaxation and cell cycle control outside the lower urinary tract. Here, we investigated the expression and function of EPAC in human prostate tissues from patients undergoing radical prostatectomy. Results: mRNA and protein expression of EPAC was detected in all prostate tissues by RT-PCR and Western blot analysis. Immunoreactivity was observed in stromal cells, and colocalized with immunofluorescence for a-smooth muscle actin and calponin. Under normal conditions, noradrenaline-or phenylephrine-induced contraction of prostate strips in the organ bath was not affected by the EPAC activator pCPT (SP-8-pCPT-2'-O-Me-cAMPS.NA) (30 mu M). However, when the cyclooxygenase inhibitor indomethacin (50 mu M) was added, EPAC activators pCPT and OME (8-CPT-2'-O-Me-cAMP.Na) (30 mu M) significantly reduced contractions by low concentrations of phenylephrine. These effects were not observed on noradrenaline-induced contraction. OME and pCPT caused phosphorylation of the transcription factor Elk1 in prostate tissues. Elk1 activation was confirmed by EMSA (electrophoretic mobility shift assay), where OME and pCPT incresed Elk1 binding to a specific DNA probe. Conclusions: EPAC activation may reduce alpha 1-adrenergic prostate contraction in the human prostate, although this effect is masked by cyclooxygenases and beta-adrenoceptors. A main EPAC function in the human prostate may be the regulation of the transcription factor Elk1.

Hennenberg, M., et al. (2011). "alpha 1-adrenoceptor activation induces phosphorylation of beta 2-adrenoceptors in human prostate tissue." Bju International 108(6): 922-928.

OBJECTIVE To test whether beta 1-adrenoceptor activation leads to phosphorylation of the beta 2-adrenoceptor in human prostate tissue. PATIENTS AND METHODS Prostate tissue from patients undergoing radical prostatectomy was stimulated in vitro with the alpha 1-adrenergic agonist phenylephrine (10 mu M). alpha 2-adrenoceptor phosphorylation at serines 345/346 was studied using Western blot analysis with a phospho-specific antibody. The role of second messenger kinases was assessed by studying the effects of the protein kinase C (PKC) inhibitor Ro 31-8425 and the protein kinase A (PKA) inhibitor H89 on phenylephrine-induced phosphorylation. The expression of G protein-coupled receptor kinases (GRKs) 2/3 was analysed using quantitative reverse-transcriptase-polymerase chain reaction (RT-PCR), Western blot analysis and immunohistochemistry. RESULTS Stimulation of prostate tissue with phenylephrine resulted in phosphorylation of the beta 2-adrenoceptor (5, 10 and 20 min after stimulation). This alpha 1-adrenoceptor-induced phosphorylation of beta 2-adrenoceptors was resistant to inhibition of PKC and PKA. Changes in phosphorylation levels were not attributable to changes in receptor levels, as these remained constant during stimulation. RT-PCR and Western blot analysis showed expression of GRK2/3 in human prostate tissues. Immunohistochemical staining showed that GRK2/3 expression in human prostate tissue is located to stromal and smooth muscle cells. CONCLUSIONS Activation of alpha 1-adrenoceptors causes phosphorylation of beta 2-adrenoceptors in the human prostate. This may enhance alpha 1-adrenergic contraction and is possibly mediated by GRK2, which is expressed in prostate smooth muscle. Mutual regulation between different adrenergic receptors might be involved in the therapeutic effects of alpha 1-blockers in patients with benign prostate hyperplasia.

Herawi, M. and J. I. Epstein (2007). "Solitary fibrous tumor on needle biopsy and transurethral resection of the prostate - A clinicopothologic study of 13 cases." American Journal of Surgical Pathology 31(6): 870-876.

One of the least commonly encountered spindle cell tumors seen on prostatic needle biopsy or transurethral resection (TUR) of the prostate is solitary fibrous tumor (SFT). We studied 13 cases of SFTs identified on either prostate needle biopsy (n = 9) or TUR of the prostate (n = 4). Mean patient age at diagnosis was 63 years (range: 46 to 75 y; median: 65 y). Twelve men presented with urinary tract symptoms and I patient was biopsied during work-up of bone metastases. Ten cases were SFTs originating in the prostate, 2 cases arose between the prostate and rectum extending into the prostate (n = 2), and I case was a pelvic mass without infiltration of the prostate. In 9 cases, a complete tumor resection was attempted by cystoprostatectomy (n = 2), radical prostatectomy (n = 4), pelvic exenteration (n = 2), or pelvic tumor resection (n = 1). Enucleation (n = 1) and TUR (n = 1) were performed in 2 other cases. Tumor sizes ranged from 8.5 to 15cm in 7 radically resected cases. Mitotic rates were 3 to 5 per 10 high power fields in 5 cases, with the remaining cases having either rare (n = 4) or no mitoses (n 4). Seven cases demonstrated areas of necrosis. Based on a combination of increased cellularity, mitotic activity, necrosis, nuclear pleomorphism, and infiltrativeness, 4 prostatic SFTs were malignant, 4 were benign, and 2 were borderline. Of the 3 non-prostatic SFTs, I was malignant and 2 were borderline. All tumors but I were immunoreactive for CD34 (n = 12). Material for additional immunohistochemistry was available for the majority of cases with positive stains for Bcl-2 (11/11), CD99 (7/10), beta-catenin (5/10), and c-kit (0/11). Three SFTs demonstrated >= 10% p53 immunoreactivity including 1 tumor with 50% positivity; and 3 cases had Ki-67 rates of >= 20%. Although all SFTs were initially clinically considered to be of prostatic origin, some of the cases arose in the pelvis with secondary involvement of the prostate. Approximately 50% of prostatic SFTs were malignant. Even in the prostatic and nonprostatic SFTs with no overt malignant features, sometimes it was necessary to remove the prostate and in some instances the adjacent organs because of the large size of the tumors. SFTs must be differentiated from other spindle cell neoplasms of the prostate especially from gastrointestinal stromal tumors that may arise from the rectal wall with invasion of the prostate or from the region between the rectum and the prostate.

Hernandez, S., et al. (2009). "FGFR3 mutations in prostate cancer: association with low-grade tumors." Modern Pathology 22(6): 848-856.

Prostate cancer is the second cause of cancer-related death in men of the Western World. The role of FGFR3 and its abnormalities in prostate cancer are not known. FGFR3 mutations have been reported in some human tumors. Few studies have analyzed the mutations of FGFR3 in prostate tumors, and no mutations have been previously reported. Prevalence of FGFR3 somatic mutations was investigated in a series of prostate tumors. The presence of other tumors in these patients, including urothelial, skin, colon, and lung neoplasms, was recorded. Mutational analysis of exons 7, 10, and 15 of FGFR3 revealed 9 mutations in the 112 prostate tumors studied (8%). Most of them consisted of the missense change S249C. The prevalence of mutations in tumors with combined Gleason score=6 is 18% (8/45) compared to 3% (1/36) for tumors with grade=7, and 0% (0/31) for those with grade >= 8 and metastases (P=0.007). The frequency of FGFR3 mutations in autopsy and biopsy samples was 6 and 9%, respectively. The prevalence of FGFR3 mutations in prostate tumors from patients with only prostate cancer was 2% compared to 23% in prostate tumors from patients with other associated neoplasms (P=0.001). This is the first report of molecular changes of FGFR3 in prostate cancer. This gene does not seem to be central to the pathogenesis of prostate cancer, but it is significantly associated with a subgroup of low-grade prostate tumors, and with the finding of other tumors, mainly arising in bladder and skin. Modern Pathology (2009) 22, 848-856; doi: 10.1038/modpathol.2009.46; published online 17 April 2009

Hessels, D. and J. A. Schalken (2013). "Urinary biomarkers for prostate cancer: a review." Asian Journal of Andrology 15(3): 333-339.

Although the routine use of serum prostate-specific antigen (PSA) testing has undoubtedly increased prostate cancer (PCa) detection, one of its main drawbacks is its lack of specificity. As a consequence, many men undergo unnecessary biopsies or treatments for indolent tumours. PCa-specific markers are needed for the early detection of the disease and the prediction of aggressiveness of a prostate tumour. Since PCa is a heterogeneous disease, a panel of tumour markers is fundamental for a more precise diagnosis. Several biomarkers are promising due to their specificity for the disease in tissue. However, tissue is unsuitable as a possible screening tool. Since urine can be easily obtained in a non-invasive manner, it is a promising substrate for biomarker testing. This article reviews the biomarkers for the non-invasive testing of PCa in urine.

Hessels, D., et al. (2007). "Detection of TMPRSS2-ERG fusion transcripts and prostate cancer antigen 3 in urinary sediments may improve diagnosis of prostate cancer." Clinical Cancer Research 13(17): 5103-5108.

Purpose: Early detection of prostate cancer can increase the curative success rate for prostate cancer. We studied the diagnostic usefulness of TMPRSS2-ERG fusion transcripts as well as the combination of prostate cancer antigen 3 (PCA3) RNA and TMPRSS2-ERG fusion transcripts in urinary sediments after digital rectal examination (DRE). Experimental Design: A total of 78 men with prostate cancer - positive biopsies and 30 men with prostate cancer-negative biopsies were included in this study. After DRE, the first voided urine was collected, and urinary sediments were obtained. We used semiquantitative reverse transcription-PCR (RT-PCR) analysis followed by Southern blot hybridization with a radiolabeled probe for the detection TMPRSS2-ERG fusion transcripts in these urinary sediments. A quantitative RT-PCR assay for PCA3 was used to determine the PCA3 score in the same sediments. Results: TMPRSS2-ERG fusion transcripts can be detected in the urine after DRE with a sensitivity of 37%. In this cohort of patients, the PCA3-based assay had a sensitivity of 62%. When both markers were combined, the sensitivity increased to 73%. Especially in the cohort of men with persistently elevated serum prostate-specific antigen levels and history of negative biopsies, the high positive predictive value of 94% of TMPRSS2-ERG fusion transcripts could give a better indication which patients require repeat biopsies. Conclusion: In this report, we used for the first time the combination of the prostate cancer specific biomarkers TMPRSS2-ERG and PCA3, which significantly improves the sensitivity for prostate cancer diagnosis.

Hong, Z.-f., et al. (2012). "Qianliening capsule inhibits human prostate cell growth via induction of mitochondrion-dependent cell apoptosis." Chinese Journal of Integrative Medicine 18(11): 824-830.

To investigate the molecular mechanisms by which Qianliening Capsule (a parts per thousand iaua (R) e integral a > S, QC) treats benign prostatic hyperplasia (BPH). Human prostate stromal cell line WPMY-1 was treated with 0, 1, 3 and 5 mg/mL of QC for 24, 48 and 72 h, respectively, in the presence of 10 ng/mL basic fibroblast growth factor (bFGF). The viability of WPMY-1 cells was determined by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cell morphology was observed by phase-contrast microscopy. 4',6-diamidino-2-phenylindole (DAPI) staining and fluorescence activated cell sorting (FACS) analysis with Annexin-V/propidium iodide (PI) staining were performed to determine cell apoptosis. The loss of mitochondrial membrane potential was examined by FACS analysis with 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolyl-carbocyarine iodide (JC-1) staining. Activation of caspase-3 and -9 was evaluated by colorimetric assay. The mRNA and protein expression levels of Bcl-2 and Bax were measured by reverse transcription polymerase chain reaction (RT-PCR) and Western blotting, respectively. Upon bFGF stimulation, the viability of WPMY-1 cells was increased to 122%-118% compared with the control cells (P < 0.05). However, treatment with 1-5 mg/mL of QC for 24, 48 and 72 h decreased the viability of bFGF-stimulated cells to 80%-92%, 59%-82%, 36%-62% compared with the untreated cells (P < 0.05). In addition, QC treatment reduced WPMY-1 cell density in a dose-dependent manner. Moreover, QC treatment dose-dependently induced the loss of plasma membrane asymmetry, the nuclear condensation and fragmentation, collapse of mitochondrial membrane potential, activation of caspase-9 and caspase-3, and increase of pro-apoptotic Bax/Bcl-2 ratio. Promoting mitochondrion-dependent apoptosis of prostate stromal cells might be one of the mechanisms by which QC treats BPH.

Hori, Y., et al. (2011). "Naftopidil, a Selective alpha(1)-Adrenoceptor Antagonist, Suppresses Human Prostate Tumor Growth by Altering Interactions between Tumor Cells and Stroma." Cancer Prevention Research 4(1): 87-96.

In prostate cancer, tumor-stroma interactions play a critical role in the promotion of tumorigenesis, and thus the prevention of those interactions is a promising target to suppress tumor growth. Several studies demonstrated that alpha(1)-adrenoceptor (alpha(1)-AR) antagonists, therapeutic drugs for benign prostatic hyperplasia, have growth inhibitory effects on human prostate cancer (PCa) cells through induction of apoptosis or G(1) cell-cycle arrest. However, their direct actions on stromal cells surrounding cancer cells have not yet been elucidated. In this study, we investigated the effects of subtype-selective alpha(1)-AR antagonists (naftopidil, tamsulosin, and silodosin) on prostate tumor growth with a focus on the role of stroma, using commercially available fibroblast cells (PrSC). Tumorigenic studies in vivo showed significant reductions in tumor growth when E9 cells (an androgen low-sensitive LNCaP subline) grafted with PrSC were treated with naftopidil. In in vitro analyses, naftopidil and silodosin showed antiproliferative effects on PCa cells regardless of androgen sensitivity and alpha(1)-AR subtype expression. In PrSC, a strong growth inhibitory effect was observed with naftopidil but not silodosin. Flow cytometric analysis revealed that naftopidil, but not silodosin, induced G(1) cell-cycle arrest in both PCa cells and PrSC. In naftopidil-treated PrSC, total interleukin-6 protein was significantly reduced with increased suppression of cell proliferation. Silodosin induced weak early apoptosis only in PCa cells. These findings demonstrated that naftopidil strongly suppressed cell proliferation of stromal cells, resulting in decreased tumorigenic soluble factor, suggesting that naftopidil might be effective in preventing stromal support of tumor cells. Cancer Prev Res; 4(1); 87-96. (C) 2011 AACR.

Hosseini-Beheshti, E., et al. (2012). "Exosomes as Biomarker Enriched Microvesicles: Characterization of Exosomal Proteins Derived from a Panel of Prostate Cell Lines with Distinct AR Phenotypes." Molecular & Cellular Proteomics 11(10): 863-885.

Prostate cancer is the leading type of cancer diagnosed in men. In 2010, similar to 217,730 new cases of prostate cancer were reported in the United States. Prompt diagnosis of the disease can substantially improve its clinical outcome. Improving capability for early detection, as well as developing new therapeutic targets in advanced disease are research priorities that will ultimately lead to better patient survival. Eukaryotic cells secrete proteins via distinct regulated mechanisms which are either ER/Golgi dependent or microvesicle mediated. The release of microvesicles has been shown to provide a novel mechanism for intercellular communication. Exosomes are nanometer sized cup-shaped membrane vesicles which are secreted from normal and cancerous cells. They are present in various biological fluids and are rich in characteristic proteins. Exosomes may thus have potential both in facilitating early diagnosis via less invasive procedures or be candidates for novel therapeutic approaches for castration resistance prostate cancer. Because exosomes have been shown previously to have a role in cell-cell communication in the local tumor microenvironment, conferring activation of numerous survival mechanisms, we characterized constitutive lipids, cholesterol and proteins from exosomes derived from six prostate cell lines and tracked their uptake in both cancerous and benign prostate cell lines respectively. Our comprehensive proteomic and lipidomic analysis of prostate derived exosomes could provide insight for future work on both biomarker and therapeutic targets for the treatment of prostate cancer. Molecular & Cellular Proteomics 11: 10.1074/mcp.M111.014845, 863-885, 2012.

Hwang, E.-S. and H. J. Lee (2010). "Effects of phenylethyl isothiocyanate and its metabolite on cell-cycle arrest and apoptosis in LNCaP human prostate cancer cells." International Journal of Food Sciences and Nutrition 61(3): 324-336.

Cruciferous vegetable consumption is associated with decreased risk of several cancers, including prostate cancer. Gluconasturtiin, one of the predominant glucosinolates in cruciferous vegetables, is hydrolyzed to yield phenylethyl isothiocyanate (PEITC). PEITC absorption and metabolism in humans involves glutathione conjugation followed by conversion via the mercapturic acid pathway to an N-acetylcysteine (NAC) conjugate that is excreted in the urine. We observed an inhibitory effect of PEITC and its metabolite, NAC-PEITC, on cancer cell proliferation, cell-cycle progression, and apoptosis in LNCaP human prostate cancer cells. PEITC and NAC-PEITC suppressed LNCaP cell proliferation in a dose-dependent manner, and exposure to 5 mu M PEITC or NAC-PEITC reduced cell proliferation by 25% and 30%, respectively. Cell-cycle analysis revealed that cells treated with 5 mu M PEITC or NAC-PEITC arrested at the G(2)/M phase. In addition, the percentage of cells in the S phase decreased from 46% to 25% following 48 h of incubation with PEITC or NAC-PEITC. The G(2)/M-phase cell-cycle arrest of LNCaP cells grown in the presence of PEITC or NAC-PEITC is correlated with the downregulation of Cdk1 and cyclin B(1) protein expression. Apoptosis was observed at the later stages of 24-h and 48-h treatments with 5 mu M PEITC and NAC-PEITC. In conclusion, PEITC and NAC-PEITC are potential chemopreventive/chemotherapeutic agents against LNCaP human prostate cancer cells.

Jamaspishvili, T., et al. (2010). "Urine markers in monitoring for prostate cancer." Prostate Cancer and Prostatic Diseases 13(1): 12-19.

The major advantages of urine-based assays are their noninvasive character and ability to monitor prostate cancer with heterogeneous foci. Almost all urine-detectable prostate-specific markers have been recently reviewed. For this reason, we focus here on only a few promising markers which have been independently evaluated (in particular PCA3, fusion genes, TERT, AMACR, GSTP1, MMP9 and VEGF) and very recent ones (ANXA3 and sarcosine). The emphasis is also on multiplex biomarker analysis and on microarray-based analysis of fusion genes. A combination of multiple urine biomarkers may be valuable in the case of men with persistently elevated serum prostate-specific antigen and a history of negative biopsies. The emerging urine tests should help in both early diagnosis of prostate cancer and identifying aggressive tumors for radical treatment. Prostate Cancer and Prostatic Diseases (2010) 13, 12-19; doi:10.1038/pcan.2009.31; published online 4 August 2009

Jamaspishvili, T., et al. (2011). "Quadriplex model enhances urine-based detection of prostate cancer." Prostate Cancer and Prostatic Diseases 14(4): 354-360.

BACKGROUND: The major advantages of urine-based assays are their non-invasive character and ability to monitor prostate cancer (CaP) with heterogeneous foci. While the test for the prostate cancer antigen 3 (PCA3) is commercially available, the aim of our research was to test other putative urine markers in multiplex settings (AMACR (alpha-methylacyl-CoA racemase), EZH2 (enhancer of zeste homolog 2), GOLM1 (golgi membrane protein 1), MSMB (microseminoprotein, 13), SPINK1 (serine peptidase inhibitor) and TRPM8 (transient receptor potential cation channel, subfamily M, member 8)). METHODS: Expression of the candidate biomarkers was studied in sedimented urine using quantitative reverse transcriptase polymerase chain reaction in two sets of patients with and without restriction on serum PSA levels. RESULTS: We confirmed that PCA3 is an independent predictor of cancer in the patients without restriction of serum PSA values (set 1, n = 176, PSA = 0.1-587 ng ml(-1)). However, AMACR was the only parameter that differentiated CaP from non-CaP patients with serum PSA between 3 and 15 ng ml(-1) (set 2, n = 104). The area under curve (AUC) for this gene was 0.645 with both sensitivity and specificity at 65%. Further improvement was achieved by multivariate logistic regression analysis, which identified novel duplex (TRPM8 and MSMB), triplex (plus AMACR) and quadriplex (plus PCA3) models for the detection of early CaPs (AUC = 0.665, 0.726 and 0.741, respectively). CONCLUSIONS: Novel quadriplex test could be implemented as an adjunct to serum PSA or urine PCA3 and this could improve decision making for diagnostics in the case of 'PSA dilemma' patients.

Javed, S. and S. E. M. Langley (2014). "Importance of HOX genes in normal prostate gland formation, prostate cancer development and its early detection." Bju International 113(4): 535-540.

<list list-type="bulleted" id="bju12269-list-5001"> The aims of this paper were to review the published literature on the role of HOX genes in the development of the normal prostate gland and in prostate cancer and to discuss the potential role of the HOX family member, Engrailed-2 (EN2), as a diagnostic test of PCa.Hox genes were first described in the fruit fly Drosphila melanogaster, where they specify the body plan and control the formation of body segments. They belong to a family of homeodomain-containing transcription factors that determine cell and tissue identity during normal embryonic development. They have been shown to be re-expressed by several different types of cancers. Studies have shown that different Hox genes are responsible for the development of the separate lobes of the prostate gland, the seminal vesicles and the epididymis. All HOX13 paralogues are expressed in the adult human prostate, suggesting the possibility of similarities between the function and expression of HOX genes within urological structures at similar anterior-posterior positions. The oncogenic and tumour suppressor signalling pathways associated with PCa converge on the HOX gene network, which ultimately controls gene expression, affecting tumour formation and metastatic progression. The Engrailed genes (EN1andEN2) from the HOX gene family show a very high degree of functional conservation during embryonic development. Urinary EN2 is being investigated as a potential diagnostic marker of early PCa. It is secreted into the urine by PCa cells but not by normal prostatic tissue. A recent study has shown an association between urinary EN2 levels and cancer volume in radical prostatectomy specimens. The ability to predict tumour volume could inform the treatment decision-making process for patients with localized PCa choosing between active surveillance and radical treatment options.

Jayapalan, J. J., et al. (2013). "Urine of patients with early prostate cancer contains lower levels of light chain fragments of inter-alpha-trypsin inhibitor and saposin B but increased expression of an inter-alpha-trypsin inhibitor heavy chain 4 fragment." Electrophoresis 34(11): 1663-1669.

The present study was aimed at the identification of proteins that are differentially expressed in the urine of patients with prostate cancer (PCa), those with benign prostatic hyperplasia (BPH) and age-matched healthy male control subjects. Using a combination of 2DE and MS/MS, significantly lower expression of urinary saposin B and two different fragments of inter-alpha-trypsin inhibitor light chain (ITIL) was demonstrated in the PCa patients compared to the controls. However, only one of the ITIL fragments was significantly different between the PCa and BPH patients. When image analysis was performed on urinary proteins that were transferred onto NC membranes and detected using a lectin that binds to O-glycans, a truncated fragment of inter-alpha-trypsin inhibitor heavy chain4 was the sole protein found to be significantly enhanced in the PCa patients compared to the controls. Together, these urinary peptide fragments might be useful complementary biomarkers to indicate PCa as well as to distinguish it from BPH, although further epidemiological evidence on the specificity and sensitivity of the protein candidates is required.

Jedinak, A., et al. (2015). "Novel non-invasive biomarkers that distinguish between benign prostate hyperplasia and prostate cancer." Bmc Cancer 15.

Background: The objective of this study was to discover and to validate novel noninvasive biomarkers that distinguish between benign prostate hyperplasia (BPH) and localized prostate cancer (PCa), thereby helping to solve the diagnostic dilemma confronting clinicians who treat these patients. Methods: Quantitative iTRAQ LC/LC/MS/MS analysis was used to identify proteins that are differentially expressed in the urine of men with BPH compared with those who have localized PCa. These proteins were validated in 173 urine samples from patients diagnosed with BPH (N = 83) and PCa (N = 90). Multivariate logistic regression analysis was used to identify the predictive biomarkers. Results: Three proteins, beta 2M, PGA3, and MUC3 were identified by iTRAQ and validated by immunoblot analyses. Univariate analysis demonstrated significant elevations in urinary beta 2M (P < 0.001), PGA3 (P = 0.006), and MUC3 (P = 0.018) levels found in the urine of PCa patients. Multivariate logistic regression analysis revealed AUC values ranging from 0.618 for MUC3 (P = 0.009), 0.625 for PGA3 (P < 0.008), and 0.668 for beta 2M (P < 0.001). The combination of all three demonstrated an AUC of 0.710 (95% CI: 0.631 - 0.788, P < 0.001); diagnostic accuracy improved even more when these data were combined with PSA categories (AUC = 0.812, (95% CI: 0.740 - 0.885, P < 0.001). Conclusions: Urinary beta 2M, PGA3, and MUC3, when analyzed alone or when multiplexed with clinically defined categories of PSA, may be clinically useful in noninvasively resolving the dilemma of effectively discriminating between BPH and localized PCa.

Jeong, Y.-M., et al. (2011). "Photo-activated 5-hydroxyindole-3-acetic acid induces apoptosis of prostate and bladder cancer cells." Journal of Photochemistry and Photobiology B-Biology 103(1): 50-56.

5-Hydroxyindole-3-acetic acid (5-HIAA), an indole derivative, is the main metabolite of serotonin in the human body. We determined whether or not ultraviolet B (UVB)-activated 5-HIAA (5-HIAA(UVB)) affects the viability of human prostate (LnCaP and PC-3) and bladder cancer cells (TCCSUP). While 5-HIAA alone had no cytotoxic effect at < 1 mM, 5-HIAA(UVB) induced LnCaP, PC-3, and TCCSUP cell death in a time- and dose-dependent manner. Cell cycle analysis showed that 5-HIAA(UVB) markedly increased the sub-G(0)/G(1) phase and resulted in cell cycle disruption. To elucidate the death mechanism by 5-HIAA(UVB), we examined the signal transduction pathways related to apoptosis using Western blot analysis. 5-HIAA(UVB) led to phosphorylation of stress-activated signaling proteins, such as c-Jun N-terminal kinase (INK) and/or p38 mitogen-activated protein kinase (MAPK). Furthermore, 5-HIAA(UVB) activated caspase-8, -9, and -3 and cleaved poly(ADP-ribose) polymerase (PARP), which are indicators of apoptosis. From these findings, the present study demonstrated that 5-HIAA(UVB) induces apoptotic cell death of prostate and bladder cancer cells via stress-mediated signaling and apoptotic pathways. Therefore, we suggest that 5-HIAA might be used as a new photosensitizer for photodynamic cancer therapy. (C) 2011 Elsevier B.V. All rights reserved.

Kanda, S., et al. (2009). "Loss of PTEN function may account for reduced proliferation pathway sensitivity to LY294002 in human prostate and bladder cancer cells." Journal of Cancer Research and Clinical Oncology 135(2): 303-311.

Inhibition of phosphoinositide 3 (PI3)-kinase pathway is attractive for cancer treatment. To examine the role of the phosphatase and tensin homolog (PTEN) in the development of resistance to the treatment. We cultured human prostate cancer cells (DU145 and PC-3 cells) and bladder cancer cells (EJ-1 and UM-UC-3 cells) with a PI3-kinase inhibitor, LY294002 for more than 6 weeks and cell proliferation was studied. Activation of Akt1 and ERK was examined by immunoblotting. We introduced the wild type PTEN in UM-UC-3 cells and their proliferation along with the signaling pathways was also examined. After 6 weeks, proliferation pathway sensitivity to LY294002 was reduced in cells expressing PTEN, but not in PTEN-null cells. PD98059, a MAPK/ERK kinase inhibitor, significantly inhibited proliferation of PTEN-expressing cells, but not PTEN-null cells. Stable PTEN expression in PTEN-null UM-UC-3 cells increased serum-induced ERK activation and sensitivity to PD98059-treatment, and reduced sensitivity to LY294002 after 6 weeks of exposure. Loss of PTEN function may protect against resistance to PI3-kinase inhibitors through an addiction to the PI3-kinase/Akt pathway.

Karypidis, A. H., et al. (2008). "Deletion polymorphism of the UGT2B17 gene is associated with increased risk for prostate cancer and correlated to gene expression in the prostate." Pharmacogenomics Journal 8(2): 147-151.

Metabolism of androgens includes glucuronidation, the major pathway of steroid elimination in several steroid target tissues. Glucuronidation is catalysed by UDP-glucuronosyltransferases (UGTs). UGT2B17 has been shown to be particularly active against androgens and is highly abundant in the prostate. Recently, we discovered that deletion of the UGT2B17 gene is associated with low or undetectable urinary testosterone levels. Here, we determined the phenotypic outcome of the deletion by quantifying the UGT2B17 mRNA expression in normal prostate tissues in individuals with different genotypes. Additionally, the frequency of UGT2B17 deletion polymorphism was studied in a Swedish population-based case-control study including 176 patients diagnosed with prostate cancer and 161 controls. We found that the individuals homozygous for the insertion allele expressed 30 times more UGT2B17 mRNA in prostate tissue than the heterozygotes. Carriers of the deletion allele had a significantly increased risk of prostate cancer (OR = 2.07; 95% CI = 1.32-3.25). In conclusion, these results showthe UGT2B17 deletion polymorphism is associated with prostate cancer risk.

Katafigiotis, I., et al. (2012). "Zinc alpha 2-glycoprotein as a potential novel urine biomarker for the early diagnosis of prostate cancer." Bju International 110(11B): E688-E693.
OBJECTIVE To examine the potential utility as a novel biomarker in the urine of zinc a 2-glygoprotein (ZAG) for the early diagnosis of prostate cancer. PATIENTS AND METHODS The urine of 127 consecutive candidates for a transrectal ultrasound prostatic biopsy with a mean age of 65.7 +/- 8.7 years and mean PSA 9.1 +/- 5.3 ng/mL was collected. Western blot analysis and immunohistochemistry for ZAG were performed. Receiver operating characteristic curves and logistic regression models were used to estimate the predictive ability of ZAG and to determine the optimal sensitivity and specificity by using various cut-off values for the prediction of prostate cancer. RESULTS In all, 42 patients had prostate cancer, 29 showed high grade prostatic intraepithelial neoplasia and 56 were negative. Receiver operating characteristic curve analysis showed a significant predictive ability of ZAG for prostate cancer. The area under the curve (AUC) for the prediction of prostate cancer was 0.68 (95% CI 0.59-0.78). The combination of ZAG with PSA showed a significant improvement in the predictive ability (P = 0.010), with AUC equal to 0.75 (95% CI 0.66-0.85). Separate analysis in patients with PSA levels of 4-10 ng/mL (70.1%) showed that ZAG had a discriminative power with AUC equal to 0.68. The optimal cut-off was 1.13 for ZAG, which corresponded to 6.88 times greater odds for prostate cancer. CONCLUSIONS Urine detected ZAG showed promising results in the prediction of prostate cancer. Further validation is required to establish ZAG as a novel biomarker.

Kato, T., et al. (2006). "Clinical significance of urinary white blood cell count and serum C-reactive protein level for detection of non-palpable prostate cancer." International Journal of Urology 13(7): 915-919.
Aim: The clinical significance of the urinary white blood cell (U-WBC) count and serum C-reactive protein (CRP) level was evaluated in an effort to improve the efficiency of prostate biopsies. Methods: We enrolled 228 consecutive patients with serum prostate-specific antigen (PSA) ranging from 3.0 to 20.0 ng/mL, normal digital rectal examination findings, and who underwent prostate biopsies between January 2001 and August 2004. Of these, 157 patients had histologically confirmed benign prostatic disease and the remaining 71 patients had prostate cancer. Patients with a pretreatment U-WBC count <= 3 or > 3/high power field were defined as non-pyuria and pyuria, respectively. The patients were also separated into two groups based on the serum CRP level prior to biopsy. Several clinical factors were compared among these subgroups. Results: Inflammation was histologically detected at rates of 58.1% and 34.1% in the pyuria and non-pyuria groups, respectively (P = 0.0014). The rates of cancer detection were significantly lower in the pyuria, than in the non-pyuria group (P = 0.0384). The cancer detection rates did not significantly differ according to serum CRP levels prior to biopsy. Conclusion: The U-WBC count appears to be a reliable indicator of minute prostatic inflammation. The serum PSA level was elevated in patients with asymptomatic prostatitis. Counting U-WBC is a simple, convenient and non-invasive method that should be valuable part of routine urological examinations.

Kedia, G. T., et al. (2008). "The nitric oxide pathway in the human prostate: clinical implications in men with lower urinary tract symptoms." World Journal of Urology 26(6): 603-609.

To date, there is an increasing interest in the nitric oxide (NO) pathway as a potential pharmacological target to treat male lower urinary tract symptomatology (LUTS). In the transition zone of the human prostate, a dense nitrinergic innervation has been shown of the fibromuscular stroma, glandular epithelium and blood vessels. The expression of key proteins of the NO pathway, such as the endothelial and neuronal nitric oxide synthase (eNOS, nNOS), cGMP-degrading phosphodiesterase type 5 (PDE5) and cGMP-binding protein kinase (cGK), has also been demonstrated. The hypothesis that an impaired NO/cGMP-signaling may contribute to the pathophysiology of benign prostatic hyperplasia (BPH) is supported by the results from randomized, placebo-controlled clinical studies, indicating that NO donor drugs and PDE5-inhibitors sildenafil, tadalafil and vardenafil may be useful to treat storage and voiding dysfunctions resulting from LUTS in men. Thus, given a potential role of the NO-pathway in the prostate and/or in other parts of lower urinary tract (e.g. bladder), the enhancement of the NO signaling by NO donor drugs, PDE5 inhibitors or activators of the soluble guanylyl cyclase (sGC) may represent a new therapeutic strategy for the treatment of LUTS. This review serves to focus on the role of NO and the NO-dependent signaling in the control of smooth muscle function in the human prostate. Results from clinical trials in men with LUTS/BPH are also discussed.

Keyes, M., et al. (2009). "URINARY SYMPTOM FLARE IN 712 I-125 PROSTATE BRACHYTHERAPY PATIENTS: LONG-TERM FOLLOW-UP." International Journal of Radiation Oncology Biology Physics 75(3): 649-655.

Purpose: To describe the late transient worsening of urinary symptoms ("urinary symptom Hare") in 712 consecutive prostate brachytherapy patients, associated predictive factors, association with rectal and urinary toxicity, and the development of erectile dysfunction. Methods and Materials: Patients underwent implantation between 1998 and 2003 (median follow-up, 57 months). International Prostate Symptom Score (IPSS), Radiation Therapy Oncology Group (RTOG) toxicity, and erectile function data were prospectively collected. Flare was defined as an increase in IPSS of >= 5 and of >= 8 points greater than the post-treatment nadir. The relationships between the occurrence of Hare and the patient, tumor, and treatment characteristics were examined. The Cox proportional hazards method was used to test individual variables and the multivariate models. Results: The incidence of flare was 52% and 30% using the Hare definition of an IPSS of >= 5 and >= 8 points greater than the postimplant nadir, respectively. Of the patients with symptoms, 65% had resolution of their symptoms within 6 months and 91% within I year. Flares most commonly occurred 16-24 months after implantation. On multivariate analysis, a greater baseline IPSS and greater maximal postimplant IPSS were the predictors of Hare, regardless of the flare definition used. Androgen suppression was a predictor for fewer flares (IPSS >= 5). Diabetes and prostate edema predicted for more frequent flares (IPSS >= 8). Patients with flare had a greater incidence of RTOG Grade 3 urinary toxicity and RTOG Grade 2 or greater rectal toxicity. No association was found between erectile dysfunction and the occurrence of flare. Conclusion: Urinary symptom flare is a common, transient phenomenon after prostate brachytherapy. A greater baseline IPSS and maximal postimplant IPSS were the strongest predictive factors. Flare was associated with a greater incidence of late RTOG Grade 3 urinary toxicity and greater rate of late RTOG Grade 2 or greater rectal toxicity. Crown Copyright (C) 2009 Published by Elsevier Inc.

Khan, A. P., et al. (2013). "The Role of Sarcosine Metabolism in Prostate Cancer Progression." Neoplasia 15(5): 491-+.

Metabolomic profiling of prostate cancer (PCa) progression identified markedly elevated levels of sarcosine (N-methyl glycine) in metastatic PCa and modest but significant elevation of the metabolite in PCa urine. Here, we examine the role of key enzymes associated with sarcosine metabolism in PCa progression. Consistent with our earlier report, sarcosine levels were significantly elevated in PCa urine sediments compared to controls, with a modest area under the receiver operating characteristic curve of 0.71. In addition, the expression of sarcosine biosynthetic enzyme, glycine N-methyltransferase (GNMT), was elevated in PCa tissues, while sarcosine dehydrogenase (SARDH) and pipecolic acid oxidase (PIPOX), which metabolize sarcosine, were reduced in prostate tumors. Consistent with this, GNMT promoted the oncogenic potential of prostate cells by facilitating sarcosine production, while SARDH and PIPOX reduced the oncogenic potential of prostate cells by metabolizing sarcosine. Accordingly, addition of sarcosine, but not glycine or alanine, induced invasion and intravasation in an in vivo PCa model. In contrast, GNMT knockdown or SARDH overexpression in PCa xenografts inhibited tumor growth. Taken together, these studies substantiate the role of sarcosine in PCa progression.

Killick, E., et al. (2013). "Role of Engrailed-2 (EN2) as a prostate cancer detection biomarker in genetically high risk men." Scientific Reports 3.

Controversy surrounds the use of PSA as a biomarker for prostate cancer detection, leaving an unmet need for a novel biomarker in this setting; urinary EN2 may identify individuals with clinically relevant prostate cancer. Male BRCA1 and BRCA2 mutation carriers are at increased risk of clinically significant prostate cancer and may benefit from screening. Urine samples from 413 BRCA1 and BRCA2 mutation carriers and controls were evaluated. Subjects underwent annual PSA screening with diagnostic biopsy triggered by PSA >3.0 ng/ml; 21 men were diagnosed with prostate cancer. Urinary EN2 levels were measured by ELISA and had a sensitivity of 66.7% and specificity of 89.3% for cancer detection. There was no statistically significant difference in EN2 levels according to genetic status or Gleason score. Urinary EN2 may be useful as a non-invasive early biomarker for prostate cancer detection in genetically high-risk individuals.

Kim, M. J., et al. (2008). "Acute renal failure after continuous flow irrigation in patients treated with potassium-titanyl-phosphate laser vaporization of prostate." American Journal of Kidney Diseases 51(4): E19-E24.

Cases of acute renal failure after transurethral resection of the prostate have been reported since the late 1940s. The pathogenic mechanisms postulated were acute hemolysis, renal interstitial edema, ischemic tubular injury, and rhabdomyolysis, resulting from the absorption of irrigating fluid. Because of the excellent hemostasis of the new laser techniques, absorption of irrigation fluid is supposed to be minimal. Potassium-titanyl-phosphate laser vaporization is regarded as the most recent advance in the treatment of patients with benign prostate hyperplasia, with excellent hemostatic properties. We report 3 cases of acute renal failure after continuous flow irrigation in patients treated with potassium-titanylphosphate laser vaporization. Renal failure occurred on postoperative day 1, all patients became oligoanuric 2 patients required hemodialysis therapy, and incomplete recovery of renal function was seen within 1 month. Biopsy findings were similar in all patients, consisting of widening of tubular lumens; partly containing Tamm-Horsfall protein casts, but neither hemoglobin nor myoglobin casts; flattened tubular epithelial cells with loss of brush borders; and variably edematous interstitium. During laser vaporization, irrigation pressure usually is higher than the physiological intravesical pressure and ranges from 60 to 100 mm Hg. High intravesical pressure may facilitate not only irrigating fluid absorption, but also transient urinary stasis or even vesicoureteral reflux. The latter may directly damage tubular epitheliall cells and cause acute renal failure. Thus, intravesical pressure should be kept as low as possible, even during laser prostatectomy. Am J Kidney Dis 51:e19-e24. (c) 2008 by the National Kidney Foundation, Inc.

Kim, Y., et al. (2012). "Identification of Differentially Expressed Proteins in Direct Expressed Prostatic Secretions of Men with Organ-confined Versus Extracapsular Prostate Cancer." Molecular & Cellular Proteomics 11(12): 1870-1884.

Current protocols for the screening of prostate cancer cannot accurately discriminate clinically indolent tumors from more aggressive ones. One reliable indicator of outcome has been the determination of organ-confined versus nonorgan-confined disease but even this determination is often only made following prostatectomy. This underscores the need to explore alternate avenues to enhance outcome prediction of prostate cancer patients. Fluids that are proximal to the prostate, such as expressed prostatic secretions (EPS), are attractive sources of potential prostate cancer biomarkers as these fluids likely bathe the tumor. Direct-EPS samples from 16 individuals with extracapsular (n = 8) or organ-confined (n = 8) prostate cancer were used as a discovery cohort, and were analyzed in duplicate by a nine-step MudPIT on a LTQ-Orbitrap XL mass spectrometer. A total of 624 unique proteins were identified by at least two unique peptides with a 0.2% false discovery rate. A semiquantitative spectral counting algorithm identified 133 significantly differentially expressed proteins in the discovery cohort. Integrative data mining prioritized 14 candidates, including two known prostate cancer biomarkers: prostate-specific antigen and prostatic acid phosphatase, which were significantly elevated in the direct-EPS from the organ-con-fined cancer group. These and five other candidates (SFN, MME, PARK7, TIMP1, and TGM4) were verified by Western blotting in an independent set of direct-EPS from patients with biochemically recurrent disease (n = 5) versus patients with no evidence of recurrence upon follow-up (n = 10). Lastly, we performed proof-of-concept SRM-MS-based relative quantification of the five candidates using unpurified heavy isotope-labeled synthetic peptides spiked into pools of EPS-urines from men with extracapsular and organ-confined prostate tumors. This study represents the first efforts to define the direct-EPS proteome from two major subclasses of prostate cancer using shotgun proteomics and verification in EPS-urine by SRM-MS. Molecular & Cellular Proteomics 11: 10.1074/mcp.M112.017889, 1870-1884, 2012.

Kimura, T. (2012). "East meets West: ethnic differences in prostate cancer epidemiology between East Asians and Caucasians." Chinese Journal of Cancer 31(9): 421-429.

Prostate cancer is the most prevalent cancer in males in Western countries. The reported incidence in Asia is much lower than that in African Americans and European Caucasians. Although the lack of systematic prostate cancer screening system in Asian countries explains part of the difference, this alone cannot fully explain the lower incidence in Asian immigrants in the United States and west-European countries compared to the black and non-Hispanic white in those countries, nor the somewhat better prognosis in Asian immigrants with prostate cancer in the United States. Soy food consumption, more popular in Asian populations, is associated with a 25% to 30% reduced risk of prostate cancer. Prostate-specific antigen (PSA) is the only established and routinely implemented clinical biomarker for prostate cancer detection and disease status. Other biomarkers, such as urinary prostate cancer antigen 3 RNA, may increase accuracy of prostate cancer screening compared to PSA alone. Several susceptible loci have been identified in genetic linkage analyses in populations of countries in the West, and approximately 30 genetic polymorphisms have been reported to modestly increase the prostate cancer risk in genome-wide association studies. Most of the identified polymorphisms are reproducible regardless of ethnicity. Somatic mutations in the genomes of prostate tumors have been repeatedly reported to include deletion and gain of the 8p and 8q chromosomal regions, respectively; epigenetic gene silencing of glutathione S-transferase Pi (GSTP1); as well as mutations in androgen receptor gene. However, the molecular mechanisms underlying carcinogenesis, aggressiveness, and prognosis of prostate cancer remain largely unknown. Gene-gene and/or gene-environment interactions still need to be learned. In this review, the differences in PSA screening practice, reported incidence and prognosis of prostate cancer, and genetic factors between the populations in East and West factors are discussed.

Kinoshita, Y., et al. (2006). "Expression of prostate-specific membrane antigen in normal and malignant human tissues." World Journal of Surgery 30(4): 628-636.

Background: Prostate-specific membrane antigen (PSMA) is upregulated in androgen-dependent prostate carcinoma and it has been targeted for immunotherapy and diagnosis of this cancer. However, this protein is also expressed in other tissues. The objective of this study is to investigate its expression in normal and malignant human tissues. Methods: Using monoclonal antibodies 24.4E6 (specific for residues 638-657) and 7E11.C5 (specific for the transmembrane domain of PSMA), immunohistochemical detection of PSMA was performed in surgical specimens. Results: Prostate-specific membrane antigen was detected in the epithelium of prostate, urinary bladder, proximal tubules of kidney, liver, esophagus, stomach, small intestine, colon, breast, fallopian tubes and testicular seminiferous tubules, hippocampal neurons and astrocytes, ependyma, cortex and medulla of the adrenal gland, and ovary stroma. It was also detected in neoplasms of the prostate, kidney, urinary bladder, stomach, small intestine, colon, lung, adrenal gland, and testis. It was not detected in normal seminal vesicles or the lung. Conclusions: These findings demonstrate that PSMA is widely distributed in normal tissues, and, depending on the tumors, its expression is up- or down-regulated, or unchanged. The broad distribution of PSMA may make it suitable for the diagnosis and therapy of a wide variety of tumors.

Kiprijanovska, S., et al. (2014). "Mapping and Identification of the Urine Proteome of Prostate Cancer Patients by 2D PAGE/MS." International journal of proteomics 2014: 594761-594761.

Proteome analysis of the urine has shown that urine contains disease-specific information for a variety of urogenital system disorders, including prostate cancer (PCa). The aim of this study was to determine the protein components of urine from PCa patients. Urine from 8 patients with clinically and histologically confirmed PCa was analyzed by conventional 2D PAGE. The MS identification of the most prominent 125 spots from the urine map revealed 45 distinct proteins. According to Gene Ontology, the identified proteins are involved in a variety of biological processes, majority of them are secreted (71%), and half of them are enzymes or transporters. Comparison with the normal urine proteome revealed 11 proteins distinctive for PCa. Using Ingenuity Pathways Analysis, we have found 3 proteins (E3 ubiquitin-protein ligase rififylin, tumor protein D52, and thymidine phosphorylase) associated with cellular growth and proliferation (p = 8.35 * 10(-4) - 3.41 * 10(-2)). The top network of functional associations between 11 proteins was Cell Death and Survival, Cell-To-Cell Signaling and Interaction, and System Development and Function (p = 10(-30)). In summary, we have created an initial proteomic map of PCa patient's urine. The results from this study provide some leads to understand the molecular bases of prostate cancer.

Kohaar, I., et al. (2013). "Genetic Variant as a Selection Marker for AntiProstate Stem Cell Antigen Immunotherapy of Bladder Cancer." Journal of the National Cancer Institute 105(1): 69-73.

A monoclonal antibody against prostate stem cell antigen (PSCA) has emerged as a novel cancer therapy currently being tested in clinical trials for prostate and pancreatic cancers, but this treatment is likely to be efficient only in patients with PSCA-expressing tumors. The present study demonstrates that a genetic variant (rs2294008) discovered by bladder cancer genome-wide association studies is a strong predictor of PSCA protein expression in bladder tumors, as measured by two-sided multivariable linear regression (P 6.4610(11); n 278). The association pattern is similar in non-muscle-invasive tumors, stages Ta (P 3.1010(5); n 173) and T1 (P 2.6410(5); n 60), and muscle-invasive tumors, stages T2 (P .01; n 23) and T3/4 (P .03; n 22). The study suggests that anti-PSCA immunotherapy might be beneficial for bladder cancer patients with high tumor PSCA expression, which is statistically significantly associated with the presence of CT and TT genotypes of a common genetic variant, rs2294008. Future clinical studies will be needed to validate PSCA as a therapeutic target for bladder cancer.

Konwar, R., et al. (2010). "Glutathione S-transferase Gene Variants and Risk of Benign Prostate Hyperplasia in a North Indian Population." Asian Pacific Journal of Cancer Prevention 11(2): 365-370.

Glutagthione S-transferase (GST) is over-expressed in benign prostate hyperplasia (BPH) patients, but the significance of GST polymorphisms for susceptibility to diseases of the prostate is unclear. The objectives of this study were to determine relationships between polymorphisms in the GSTM1, T1 and P1 genes with risk of symptomatic BPH and influence on standard therapy. A gene polymorphism association study conducted with 160 symptomatic BPH patients with BPE (benign prostatic enlargement) and LUTS (lower urinary tract symptoms) and 200 age-matched controls. Patient inclusion criteria are age >50 years prostate size >30cm(3), AUA (American urological association) score >7 and PVR volume <= 200 ml. Patients were treated with alpha-adrenergic blockers and 5 alpha-reductase inhibitors for 6 months and subdivided based on their significant improvement in parameters between pre and post 6 month combined therapy to study associations with the GST polymorphisms. The GSTT1 and GSTM1 variants genotyped with multiplex-PCR, whereas GSTP1 polymorphisms were determined with PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism). We observed a lack of any association with the GSTT1 (p=0.45, OR=2.25, 95% CI=1.71-2.22) and GSTP1 (p=0.92 and 0.99) genes. However, there was a significant link with the null alleles of the GSTM1 (p=0.000, OR=2.24, 95% CI=1.46-3.42) gene. The combined analysis of the three genotypes demonstrated further increase in the risk of symptomatic BPH (p=0.009, OR=8.31 95% CI=1.71-40.37). Polymorphisms of GST genes were not associated with responders or non-responders. Thus the GSTM1 deletion polymorphism is significantly associated with increased risk of symptomatic BPH, but none of the genes appearedto influence response to standard BPH therapy.

Korzeniewski, N., et al. (2015). "Identification of cell-free microRNAs in the urine of patients with prostate cancer." Urologic oncology 33(1): 16.e17-22.

OBJECTIVES: Current methods for the early detection of prostate cancer (PCa), in particular prostate-specific antigen screening, are likely to benefit from complementary molecular analyses to enhance specificity. MicroRNAs (miRNA) are small endogenously expressed noncoding RNAs that negatively regulate the expression of protein-coding genes at the transcriptional or translational level. Accumulating evidence suggests that miRNAs play an important role in tumorigenesis, are differentially expressed in different cancer types, and can be found in all bodily fluids so-far tested, including urine. METHODS AND MATERIALS: This study was undertaken to determine if miRNA could be isolated from the cell-free fraction of freely voided urine of PCa patients and if a miRNA signature could be found that would identify patients with cancer. RESULTS: In a first set of proof-of-concept experiments, we isolated RNA from the supernatant of cultured PCa cells, as well as cellular RNA, and compared the expression of cell-free miRNAs vs. cellular miRNAs. We identified miRNA-483-5p, miRNA-1275, and miRNA-1290 among the most abundant cell-free miRNAs. We then tested the expression of these miRNAs in patient urine samples. A total of 18 patients without detectable PCa by transperineal template-saturation biopsy and 71 patients with diagnosed biopsy-proven PCa were retrospectively analyzed. We could confirm that cell-free miRNAs found in cultures of PCa cells can in fact be isolated from freely voided patients' urine. Furthermore, we found that patients with PCa express miR-483-5p in the cell-free urine fraction at a higher level than control patients do. CONCLUSIONS: The present study is among the first to show that miRNAs can be detected in the cell-free, non-exosome-enriched fraction of urine collected from patients with PCa. As the method used here does not require isolation of exosomes, it could potentially simplify the future use of miRNAs as urine-based biomarkers.

Koutalellis, G., et al. (2012). "L-dopa decarboxylase (DDC) gene expression is related to outcome in patients with prostate cancer." Bju International 110(6B): E267-E273.

What's known on the subject? and What does the study add? L-dopa decarboxylase (DDC) has been documented as a novel co-activator of androgen receptor transcriptional activity. Recently, it was shown that DDC gene expression is significantly higher in patients with PCa than in those with BPH. In the present study, there was a significant association between the DDC gene expression levels and the pathological stage and Gleason score of patients with prostate cancer (PCa). Moreover, DDC expression was shown to be an unfavourable prognostic marker of biochemical recurrence and disease-free survival in patients with PCa treated by radical prostatectomy. OBJECTIVE To determine whether L-dopa decarboxylase gene (DDC) expression levels in patients with prostate cancer (PCa) correlate to biochemical recurrence and disease prognosis after radical prostatectomy (RP). PATIENTS AND METHODS The present study consisted of 56 samples with confirmed malignancy from patients with PCa who had undergone RP at a single tertiary academic centre. Total RNA was isolated from tissue specimens and a SYBR Green fluorescencebased quantitative real-time polymerase chain reaction methodology was developed for the determination of DDC mRNA expression levels of the tested tissues. Follow-up time ranged between 1.0 and 62.0 months (mean +/- SE, 28.6 +/- 2.1 month; median, 31.5 months). Time to biochemical recurrence was defined as the interval between the surgery and the measurement of two consecutive values of prostate-specific antigen (PSA) = 0.2 ng/mL. RESULTS DDC expression levels were found to be positively correlated with the tumour-node-metastasis stage (P = 0.021) and Gleason score (P = 0.036) of the patients with PCa. Patients with PCa with raised DDC expression levels run a significantly higher risk of biochemical recurrence after RP, as indicated by Cox proportional regression analysis (P = 0.021). Multivariate Cox proportional regression models revealed the preoperative PSA-, age-and digital rectal examinationin-dependent prognostic value of DDC expression for the prediction of disease-free survival (DFS) among patients with PCa (P = 0.036). Kaplan-Meier survival analysis confirms the significantly shorter DFS after RP of PCa with higher DDC expression levels (P = 0.015). CONCLUSIONS This is the first study indicating the potential of DDC expression as a novel prognostic biomarker in patients with PCa who have undergone RP. For further evaluation and clinical application of the findings of the present study, a direct analysis of mRNA and/or its protein expression level in preoperative biopsy, blood serum and urine should be conducted.

Kovacs, G. L. (2014). "New challenges and earlier approved methods in the laboratory diagnosis of prostate cancer." Magyar onkologia 58(4): 301-309.

Prostate cancer is usually a disease of elderly men, however, over 40 years of age the tumor can appear at any times. PSA is a protein molecule synthesized by prostate cells. Measurement of serum PSA has revolutionized the diagnosis and treatment of prostate cancer. However, PSA is not sufficiently specific for the detection of prostate cancer, since serum PSA might also be elevated in benign prostate diseases, as well as following physical stimulation of the gland (digital rectal examination, biopsy, catheterization, or even ejaculation). To increase the specificity of PSA, different derivative parameters have been developed i.e. PSA density (ratio of PSA to prostate volume), PSA velocity (change of PSA over a time period) or age-specific reference ranges. 65-95% of circulating PSA is bound to different proteins, while the rest of PSA circulates in a non-bound form (free PSA, fPSA). In addition to fPSA, the prostate health index [phi; (-2)proPSA/fPSA*PSA] is increasingly used to differentiate between carcinoma-induced and non-carcinoma-induced increase in PSA. PCA3 is a non-coding messenger RNA, which is 60-70-fold overexpressed by cancer cells in the prostate. Measurement of urine PCA3 appears to be more sensitive than %tPSA, and is independent of prostate volume, age or tPSA. The author reviews laboratory biomarkers related to prostate cancer, used either in the routine clinical practice, or in research. Laboratory biomarkers seem to be useful tools to reduce the incidence of advanced stage, or metastatic prostate cancer, and the cancer-related death rate. A promising perspective for the future is the detection of circulating prostate cancer cells and the profiling of microRNAs, especially on the field of tumor prognosis.

Kristal, A. R., et al. (2008). "Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: Results from the prostate cancer prevention trial." American Journal of Epidemiology 167(8): 925-934.

This study examined dietary risk factors for incident benign prostatic hyperplasia (BPH) in 4,770 Prostate Cancer Prevention Trial (1994-2003) placebo-arm participants who were free of BPH at baseline. BPH was assessed over 7 years and was defined as medical or surgical treatment or repeated elevation (>14) on the International Prostate Symptom Score questionnaire. Diet, alcohol, and supplement use were assessed by use of a food frequency questionnaire. There were 876 incident BPH cases (33.6/1,000 person-years). The hazard ratios for the contrasts of the highest to lowest quintiles increased 31% for total fat and 27% for polyunsaturated fat and decreased 15% for protein (all p(trend) < 0.05). The risk was significantly lower in high consumers of alcoholic beverages (0 vs. >= 2/day: hazard ratio (HR) = 0.67) and vegetables (< 1 vs. >= 4/day: HR = 0.68) and higher in daily (vs. <1/week) consumers of red meat (HR = 1.38). There were no associations of supplemental antioxidants with risk, and there was weak evidence for associations of lycopene, zinc, and supplemental vitamin D with reduced risk. A diet low in fat and red meat and high in protein and vegetables, as well as regular alcohol consumption, may reduce the risk of symptomatic BPH.

Kristiansen, G. (2009). "Immunohistochemical algorithms in prostate diagnostics: what's new?" Der Pathologe 30 Suppl 2: 146-153.

Immunohistochemistry has become an indispensible tool in biopsy diagnostics of prostate tissues. In particular the use of basal cell markers can be useful to differentiate benign and malignant lesions as a lack of basal cells is considered a hallmark of malignancy. Basal cell cytokeratins and p63 have therefore a long standing place in the diagnostic portfolio of most genito-urinary pathologists. However, to complement the use of these negative markers by additional positive immunohistochemistry markers of malignancy would be desirable to further increase diagnostic accuracy. The most widely used positive marker is alpha-methylacyl-CoA racemase (AMACR), which is strongly upregulated in prostate cancer and which can even be combined with p63 in a single immunostaining. This article briefly and critically reviews current diagnostic prostate cancer biomarkers and also suggests golgi phosphoprotein 2 (GOLPH2) and fatty acid synthase (FASN) as additional diagnostic markers.

Kundu, S. D., et al. (2008). "The toll-like receptor pathway: A novel mechanism of infection-induced carcinogenesis of prostate epithelial cells." Prostate 68(2): 223-229.

BACKGROUND. Inflammation and infection have been linked to the pathogenesis of many cancers including Prostate cancer. Components of bacteria and viruses have been identified within pathological specimens of men with prostate cancer. METHODS. We characterized the in vitro response of benign prostate epithelial cells to components of infectious agents as they relate to toll-like receptors. RESULTS. Primary and immortalized prostate epithelial cells (RWPE) exhibited increased proliferation in response to exposure to lipopolysaccharide (LPS) and CpG DNA. These molecules are well-characterized surrogates for gram negative bacteria (e.g., E. coh) and DNA viruses (e.g., HPV and HSV), which are common in the genitourinary system. Our experiments show that RWPE cells express both TLR 4 (LPS-specific) and TLR 9 (CpG-specific). Targeted knock down of individual TLR expression using siRNA abrogated the proliferative response of RWPE cells to LPS and CpG, respectively. In addition, compared to non-stimulated cells, LPS and CpG up-regulate active NF-kappa B expression. Increased NF-kappa B activation was confirmed using RWPE cells that were stably transfected with a NF-kappa B reporter construct. Interestingly, NF-kappa B activation was both concentration- and time-dependent when stimulated with LPS. RWPE cells were less susceptible to TNF-alpha induced apoptosis as measured by TUNEL staining when stimulated with CpG or LPS. High concentrations of LPS also prevented cell death as measured by LDH release. CONCLUSIONS. Our study has identified a unique mechanism that describes how components of pathogens common in the urinary system may contribute to the malignant transformation of benign prostate epithelia.

Kunit, T., et al. (2014). "Inhibition of smooth muscle force generation by focal adhesion kinase inhibitors in the hyperplastic human prostate." American Journal of Physiology-Renal Physiology 307(7): F823-F832.

Smooth muscle contraction may be critical for lower urinary tract symptoms (LUTS) in patients with benign prostate hyperplasia and requires stable anchorage of the cytoskeleton to the cell membrane. These connections are regulated by focal adhesion kinase (FAK). Here, we addressed the involvement of FAK in the regulation of smooth muscle contraction in hyperplastic human prostate tissues. Prostate tissues were obtained from radical prostatectomy. Expression of FAK and focal adhesion proteins was assessed by Western blot analysis and immunohistochemical stainings. Effects of the FAK inhibitors PF-573228 and Y-11 on contraction of prostate strips were examined in the organ bath. Expression of FAK and focal adhesion proteins (integrin-5 alpha, paxilin, and c-Src) was detected by Western blot analysis in prostate samples. By double immunofluorescence staining with calponin and pan-cytokeratin, expression of FAK was observed in stromal and epithelial cells. Immunoreactivity for FAK colocalized with integrin-5 alpha, paxilin, talin, and c-Src. Stimulation of prostate tissues with the alpha 1-adrenergic agonist phenylephrine increased the phosphorylation state of FAK at Tyr(397) and Tyr(925) with different kinetics, which was blocked by the alpha 1-adrenoceptor antagonist tamsulosin. Norepinephrine and phenylephrine induced concentration-dependent contractions of prostate strips. Both FAK inhibitors PF-573228 and Y-11 significantly inhibited norepinephrine-and phenylephrine-induced contractions. Finally, PF-573228 and Y-11 inhibited contractions induced by electric field stimulation, which was significant at the highest frequency. In conclusion, alpha 1-adrenergic smooth muscle contraction or its regulation involves FAK in the human prostate. Consequently, FAK may be involved in the pathophysiology of LUTS and in current or future LUTS therapies.

Kunju, L. P., et al. (2006). "Prostate-specific antigen, high-molecular-weight cytokeratin (Clone 34 beta E12), and/or p63 - An optimal Immunohistochemical panel to distinguish poorly differentiated prostate adenocarcinoma from urothelial carcinoma." American Journal of Clinical Pathology 125(5): 675-681.

An optimal immunohistochemical panel to distinguish poorly differentiated prostate (PCa),from urothelial (UCa) carcinoma was selected from. a panel consisting of prostate-specific antigen. (PSA) and prostatic acid phosphatase (PAP), high-molecular-weight cytokeratin (HMWCK) (clone 34 beta E12), cytokeratin (CK) 7, CK20, p63, and alpha-methylacylcoenzyme A racemase. The pilot group was composed of poorly differentiated UCa (n = 36) and PCa (n = 42). PSA and PAP stained 95% of PCa vs 0% and 11% of UCa cases, respectively. HMWCK and p63 stained 97% and 92% of UCa vs 2% and 0% of PCa cases respectively. CK7/CK20 coexpression was noted in 50% of UCa cases, whereas 86% of PCa cases were negative with both. A panel of PSA, HMWCK, and p63 was optimal for separating 95% PCa (PSA+/HMWCK and/or p63-) v.s 97% UCa (PSA-/HMWCK and/or p63+). This panel was used on 26 diagnostically challenging cases and resolved 81% of cases as UCa vs PCa. The majority of PCa cases retain PSA. Negative PSA with positive HMWCK and/or p63 establishes cc diagnosis of UCa.

Kurahashi, T., et al. (2010). "Characterization of prostate cancer incidentally detected in radical cystoprostatectomy specimens from Japanese men with bladder cancer." International Urology and Nephrology 42(1): 73-79.

The objective of this study was to investigate and characterize the clinicopathological features of incidentally detected prostate cancer in radical cystoprostatectomy specimens from Japanese men with bladder cancer. We reviewed the pathological reports of 251 male patients who underwent radical cystoprostatectomy for bladder cancer at our institution and identified men with incidentally detected prostate cancer in these specimens. Clinicopathological data of patients with incidental prostate cancer in cystoprostatectomy specimens (group A) were compared with those of 193 patients with clinically detected prostate cancer who underwent radical prostatectomy (group B). Immunohistochemical staining was also performed to measure the expression levels of Ki-67, p53 and androgen receptor (AR) proteins in specimens from both groups A and B. In this series, a total of 31 patients (12.3%; group A) were incidentally diagnosed as having prostate cancer in radical cystoprostatectomy specimens. Clinically significant cancer, defined as any tumor greater than 0.5 cc according to the report by Stamy et al. (Cancer 71:933-938, 1993) was detected in 9 (29.0%) in group A and 170 (88.1%) in group B. Mean age in group A was significantly older than that in group B, while despite the lack of significant difference in the incidence of seminal vesicle invasion between these two groups, other parameters in group A were significantly more favorable than those in group B, including serum prostate-specific antigen, pathological stage, Gleason score, perineural invasion and capsular penetration. None of the patients in group A had biochemical recurrence (median observation period, 82 months); however, biochemical recurrence occurred in 41 (21.2%) in group B (median observation period, 46 months). Furthermore, immunohistochemical study demonstrated the significantly greater expression of Ki-67, p53 and AR proteins in group B than in group A. Clinicopathological features of incidentally detected prostate cancer are markedly more favorable than those of clinically detected prostate cancer, which may reflect less aggressive biological phenotypes of incidental prostate cancer arising in Japanese men.

Langsenlehner, T., et al. (2011). "Association between single nucleotide polymorphisms in the gene for XRCC1 and radiation-induced late toxicity in prostate cancer patients." Radiotherapy and Oncology 98(3): 387-393.
Background and purpose: Polymorphisms in genes responsible for DNA damage signaling and repair might modulate DNA repair capacity and, therefore, affect cell and tissue response to radiation and influence individual radiosensitivity. The purpose of the present prospective investigation was to evaluate the association of single nucleotide polymorphisms in XRCC1 with radiation-induced late side effects in prostate cancer patients treated with radiotherapy. Material and methods: To analyze the role of XRCC1 polymorphisms for late toxicity 603 participants from the Austrian PROCAGENE study treated with three-dimensional conformal radiotherapy were included in the present investigation. Three non-synonymous candidate polymorphisms in the X-ray repair cross-complementing group 1 (XRCC1) gene (Arg194Trp; Arg280His; Arg399Gln) were selected and determined by 5-nuclease (TaqMan) assays. Results: Within a median follow-up time of 35 months, 91 patients (15.7%) developed high-grade late toxicities (defined as late bladder and/or rectal toxicity RTOG >= 2). In a Kaplan-Meier analysis, carriers of the XRCC1 Arg280His polymorphism were at decreased risk of high-grade late toxicity (p = 0.022), in multivariate analysis including clinical and dosimetric parameters as potential confounders the XRCC1 Arg280His polymorphism remained a significant predictor for high-grade late toxicity (HR = 0.221, 95% CI 0.051-0.956; p = 0.043). No significant associations were found for the remaining polymorphisms. Conclusions: We conclude that the XRCC1 Arg280His polymorphism may be protective against the development of high-grade late toxicity after radiotherapy in prostate cancer patients. (C) 2011 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 98 (2011) 387-393

Langsenlehner, T., et al. (2011). "Impact of VEGF Gene Polymorphisms and Haplotypes on Radiation-Induced Late Toxicity in Prostate Cancer Patients." Strahlentherapie Und Onkologie 187(12): 784-791.

Background and Purpose: Vascular endothelial growth factor (VEGF) is an important determinant of microvascular permeability and angiogenesis and has been shown to be up-regulated during the late phase of radiation injury. The present prospective study was performed to evaluate the role of VEGF gene polymorphisms and haplotypes in the development of radiation-induced late side effects in prostate cancer patients. Patients and Methods: The association of VEGF gene polymorphisms and haplotypes with high-grade late rectal or urinary toxicity (defined as late toxicity EORTC/RTOG >= 2) was analyzed using 493 prostate cancer patients from the Austrian PROCAGENE study treated with definitive radiotherapy. Seven candidate polymorphisms in the VEGF gene were selected and determined by 5'-nuclease (TaqMan) assays. Results: Within a median follow-up time of 48 months, 42 patients (8.6%) developed high-grade late rectal and 47 patients (9.6%) urinary toxicity, respectively. In a Kaplan-Meier analysis, carriers of the VEGF -7C > T polymorphism were at increased risk of high-grade late rectal toxicity (p = 0.003) and in a multivariate analysis including clinical and dosimetric parameters as potential confounders the VEGF -7C > T polymorphism remained a significant predictor (HR = 2.8,95% CI 1.349-5.813; p = 0.006). Furthermore, the ATTGT haplotype formed by five polymorphisms upstream of the coding sequence demonstrated a significant association with late rectal toxicity grade >= 2 (p = 0.001). No significant associations were found for the remaining polymorphisms and haplotypes. Conclusion: We conclude that genetic variants in the VEGF gene may influence the risk of high-grade late rectal toxicity after definitive radiotherapy for prostate cancer.

Laxman, B., et al. (2008). "A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer." Cancer Research 68(3): 645-649.

Although prostate-specific antigen (PSA) serum level is currently the standard of care for prostate cancer screening in the United States, it lacks ideal specificity and additional biomarkers are needed to supplement or potentially replace serum PSA testing. Emerging evidence suggests that monitoring the noncoding RNA transcript PCA3 in urine may be useful in detecting prostate cancer in patients with elevated PSA levels. Here, we show that a multiplex panel of urine transcripts outperforms PCA3 transcript alone for the detection of prostate cancer. We measured the expression of seven putative prostate cancer biomarkers, including PCA3, in sedimented urine using quantitative PCR on a cohort of 234 patients presenting for biopsy or radical prostatectomy. By univariate analysis, we found that increased GOLPH2, SPINK1 and PCA3 transcript expression and TMPRSS2:ERG fusion status were significant predictors of prostate cancer. Multivariate regression analysis showed that a multiplexed model, including these biomarkers, outperformed serum PSA or PCA3 alone in detecting prostate cancer. The area under the receiver-operating characteristic curve was 0.758 for the multiplexed model versus 0.662 for PCA3 alone (P = 0.003). The sensitivity and specificity for the multiplexed model were 65.9% and 76.0%, respectively, and the positive and negative predictive values were 79.8% and 60.8%, respectively. Taken together, these results provide the framework for the development of highly optimized, multiplex urine biomarker tests for more accurate detection of prostate cancer.

Laxman, B., et al. (2006). "Noninvasive detection of TMPRSS2 : ERG fusion transcripts in the urine of men with prostate cancer." Neoplasia 8(10): 885-888.

We recently reported the identification of recurrent gene fusions in the majority of prostate cancers involving the 5' untranslated region of the androgen-regulated gene TMPRSS2 and the ETS family members ERG, ETV1, and ETV4. Here we report the noninvasive detection of these gene fusions in the urine of patients with clinically localized prostate cancer. By quantitative polymerase chain reaction, we assessed the expression of ERG and TMPRSS2: ERG transcripts in urine samples obtained after prostatic massage from 19 patients (11 prebiopsy and 8 pre-radical prostatectomy) with prostate cancer. We observed a strong concordance between ERG overexpression and TMPRSS2: ERG expression, with 8 of 19 (42%) patients having detectable TMPRSS2: ERG transcripts in their urine. Importantly, by fluorescence in situ hybridization, we confirmed the presence or the absence of TMPRSS2: ERG gene fusions in matched prostate cancer tissue samples from three of three patients with fusion transcripts in their urine and from two of two patients without fusion transcripts in their urine. These results demonstrate that TMPRSS2: ERG gene fusions can be detected in the urine of patients with prostate cancer and support larger studies on prospective cohorts for noninvasive detection of prostate cancer.

Lee, H. N., et al. (2013). "Effects of Doxazosin on Alpha 1-Adrenergic Receptors in Prostates with Benign Prostatic Hyperplasia." Luts-Lower Urinary Tract Symptoms 5(2): 82-89.

Objectives: The present study aimed to evaluate changes in mRNA and protein expression levels of 1-AR before and after doxazosin treatment. Methods: This 12-month, prospective study included males aged 50 or older who had lower urinary tract symptoms (LUTS) (International Prostate Symptom Score [IPSS] 8) with benign prostatic hyperplasia (BPH). All patients underwent transrectal ultrasound-guided prostate biopsy before and after doxazosin 4 mg medication for 12 months. The mRNA and protein expression of prostate 1-AR were analyzed using real-time quantitative reverse transcription-polymerase chain and Western blotting, respectively, before and after treatment. The clinical efficacy of doxazosin was evaluated according to changes in prostate volume, serum prostate-specific antigen (PSA) level, IPSS, quality of life (QoL) index, maximum flow rate, parameters in a voiding diary, and a Patient's Perception of Bladder Condition (PPBC) questionnaire. Results: Twenty patients aged 5072 (median age 66) with LUTS secondary to BPH completed this study. Administering doxazosin for 12 months significantly increased 1-AR protein expression in the prostate. 1-AR mRNA expression did not change significantly after doxazosin administration. IPSS, QoL index, and PPBC scores significantly improved after 12 months of doxazosin treatment. Maximal flow rate, postvoid residual urine volume (PVR), prostate volume and the parameters from the voiding diary did not change significantly after 12 months. The change of IPSS total score and LUTS were maintained until 12 months after starting treatment with doxazosin. Conclusion: Doxazosin treatment was able to increase 1-AR protein expression in the prostate. Despite increased 1-AR expression, doxazosin provides sustained, significant relief of LUTS for up to one year without a decrease in efficacy.

Lee, S., et al. (2015). "Ultrasensitive electrochemical detection of engrailed-2 based on homeodomain-specific DNA probe recognition for the diagnosis of prostate cancer." Biosensors & Bioelectronics 66: 32-38.

It is well known that the engrailed-2 (EN2) protein, a biomarker for prostate cancer, strongly binds to a specific DNA sequence (5'-TAATTA-3') to regulate transcription. Based on this intrinsic property, DNA probes with additional flanked sequences were designed and optimized. Various measurements, such as electrophoresis mobility shift assay, surface plasmon resonance, and quantitative fluorescence assay were performed to investigate the feasibility of the DNA probes. Then, the affinities of the DNA probes to the target protein were quantitatively determined using FAM-modified DNA probes and magnetic beads, resulting in dissociation constants ranging from 61.03 to 98.84 nM. To develop an early diagnosis platform for prostate cancer, an ultrasensitive electrochemical biosensor based on the electrodeposition of gold nanoparticles was designed. The EN2 protein was quantitatively detected using the electrochemical biosensor, and the calculated detection limit was found to be 5.62 fM. Finally, the specificity and applicability of the biosensor were verified using several proteins and an artificial urine medium. The impedance signals increased in the cases of EN2, suggesting that the system exhibited high selectivity to only EN2. (C) 2014 Elsevier B.V. All rights reserved.

Leeming, D. J., et al. (2008). "Does increased local bone resorption secondary to breast and prostate cancer result in increased cartilage degradation?" Bmc Cancer 8.

Background: Breast and prostate cancer patients often develop lesions of locally high bone turnover, when the primary tumor metastasizes to the bone causing an abnormal high bone resorption at this site. The objective of the present study was to determine whether local increased bone turnover in breast and prostate cancer patients is associated with an increase in cartilage degradation and to test in vitro whether osteoclasts or cathepsin K alone generate CTXII from human bone. Methods: The study included 132 breast and prostate cancer patient, where presence of bone metastases was graded according to the Soloway score. Total bone resorption (CTXI(total)) and cartilage degradation (CTXII) were determined. Results: Breast and prostate cancer patients with bone metastases revealed significant increased levels of CTXI(total) at Soloway scores 1 and higher compared to patients without bone metastases ($p < 0.001$). CTXII was statistically elevated at score 3 and 4 ($p < 0.01$). CTXII/CTXI(total) significantly decreased at score 3 and 4 ($p < 0.001$). Levels of CTXI(total), CTXII and CTXII/CTXI(total) changed + 900%, + 130%, and -90%, respectively at Soloway score 4 compared to score 0. The in vitro experiments revealed that osteoclasts released CTXI fragments but not CTXII from bone specimens. The same was observed for cathepsin K. Conclusion: Data suggest that an uncoupling between bone resorption and cartilage degradation occurs in breast and lung cancer patient.

Lewis, H., et al. (2014). "miR-888 is an expressed prostatic secretions-derived microRNA that promotes prostate cell growth and migration." Cell Cycle 13(2): 227-239.

microRNAs (miRNAs) are a growing class of small non-coding RNAs that exhibit widespread dysregulation in prostate cancer. We profiled miRNA expression in syngeneic human prostate cancer cell lines that differed in their metastatic potential in order to determine their role in aggressive prostate cancer. miR-888 was the most differentially expressed miRNA observed in human metastatic PC3-ML cells relative to non-invasive PC3-N cells, and its levels were higher in primary prostate tumors from cancer patients, particularly those with seminal vesicle invasion. We also examined a novel miRNA-based biomarker source called expressed prostatic secretions in urine (EPS urine) for miR-888 expression and found that its levels were preferentially elevated in prostate cancer patients with high-grade disease. These expression studies indicated a correlation for miR-888 in disease progression. We next tested how miR-888 regulated cancer-related pathways in vitro using human prostate cancer cell lines. Overexpression of miR-888 increased proliferation and migration, and conversely inhibition of miR-888 activity blocked these processes. miR-888 also increased colony formation in PC3-N and LNCaP cells, supporting an oncogenic role for this miRNA in the prostate. Our data indicates that miR-888 functions to promote prostate cancer progression and can suppress protein levels of the tumor suppressor genes RBL1 and SMAD4. This miRNA holds promise as a diagnostic tool using an innovative prostatic fluid source as well as a therapeutic target for aggressive prostate cancer.

Leyten, G. H. J. M., et al. (2014). "Prospective Multicentre Evaluation of PCA3 and TMPRSS2-ERG Gene Fusions as Diagnostic and Prognostic Urinary Biomarkers for Prostate Cancer." European Urology 65(3): 534-542.

Background: Prostate cancer antigen 3 (PCA3) and v-ets erythroblastosis virus E26 oncogene homolog (TMPRSS2-ERG) gene fusions are promising prostate cancer (PCa) specific biomarkers that can be measured in urine. Objective: To evaluate the diagnostic and prognostic value of Progensa PCA3 and TMPRSS2-ERG gene fusions (as individual biomarkers and as a panel) for PCa in a prospectivemulticentre setting. Design, setting, and participants: At six centres, post-digital rectal examination first-catch urine specimens prior to prostate biopsies were prospectively collected from 497 men. We assessed the predictive value of Progensa PCA3 and TMPRSS2-ERG (quantitative nucleic acid amplification assay to detect TMPRSS2-ERG messenger RNA [mRNA]) for PCa, Gleason score, clinical tumour stage, and PCa significance (individually and as a marker panel). This was compared with serum prostate-specific antigen and the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculator. In a subgroup (n = 61) we evaluated biomarker association with prostatectomy outcome. Outcome measurements and statistical analysis: Univariate and multivariate logistic regression analysis and receiver operating curves were used. Results and limitations: Urine samples of 443men contained sufficientmRNAformarker analysis. PCa was diagnosed in 196 of 443 men. Both PCA3 and TMPRSS2-ERG had significant additional predictive value to the ERSPC risk calculator parameters in multivariate analysis (p < 0.001 and resp. p = 0.002). The area under the curve (AUC) increased from 0.799 (ERSPC risk calculator), to 0.833 (ERSPC risk calculator plus PCA3), to 0.842 (ERSPC risk calculator plus PCA3 plus TMPRSS2ERG) to predict PCa. Sensitivity of PCA3 increased from68% to 76% when combinedwith TMPRSS2ERG. TMPRSS2-ERGadded significant predictive value to the ERSPC risk calculator to predict biopsy Gleason score (p < 0.001) and clinical tumour stage (p = 0.023), whereas PCA3 did not. Conclusions: TMPRSS2-ERG had independent additional predictive value to PCA3 and the ERSPC risk calculator parameters for predicting PCa. TMPRSS2-ERG had prognostic value, whereas PCA3 did not. Implementing the novel urinary biomarker panel PCA3 and TMPRSS2-ERG into clinical practice would lead to a considerable reduction of the number of prostate biopsies. (C) 2012 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Li, C., et al. (2015). "Quantitative urinary proteomics using stable isotope labelling by peptide dimethylation in patients with prostate cancer." Analytical and Bioanalytical Chemistry 407(12): 3393-3404.

Prostate cancer (PCa) is the most commonly diagnosed malignancy in men. The current prevalent diagnosis method, prostate-specific antigen (PSA) screening test, has low sensitivity, specificity and is poor at predicting the grade of disease. Thus, new biomarkers are urgently needed to improve the PCa diagnosis and staging for the management of patients. The aim of this study is to investigate the first voided urinary sample after massage for biomarker discovery for PCa. In this work, untargeted metabolomic profiling of the first voided urinary sample after massage from 28 confirmed prostate cancer patients, 20 benign enlarged prostate patients and 6 healthy volunteers was performed using liquid chromatography coupled to high-resolution tandem mass spectrometry (LC-MS/MS). Single and multiple peptide protein and cross-linking molecules were identified using PEAKS software. Analytical and diagnostic performance was tested using the Student's t test, Benjamini Hochberg correction and the receiver operating characteristic (ROC) curves. Using differential display analysis to compare peptides and cross-linking molecules of urinary samples between patients with benign, enlarged prostate and malignant cancer, we identified multiple peptides derived from osteopontin (SPP1) and prothrombin (F2) that are lower in PCa patients than in benign and enlarged prostate. The diagnosis accuracies of SPP1 and F2 peptides are 0.65-0.77 and 0.68-0.72, respectively. In addition to this, there are significant differences between PCa and benign/enlarged prostate patients in pyridinoline (PYD) and deoxypyridinoline (DPD) (p value = 0.001). Differences also, as shown in the excretion of these molecules for different stages of PCa (p value = 0.04) as the level of DPD and DPD/PYD ratio, were high in patients with locally advanced tumours. The study underscores the importance of proteomics analysis, and our results demonstrate that a urinary-based in depth proteomic approach allows the potential identification of dysregulated pathways and diagnostic biomarkers.

Li, W., et al. (2012). "Diagnostic Significance of Overexpression of Golgi Membrane Protein 1 in Prostate Cancer." Urology 80(4).

OBJECTIVE To investigate the diagnostic significance of Golgi membrane protein 1 (GOLM1) expression in prostate cancer. METHODS The localization of GOLM1 in prostate cancer cells was detected by immunofluorescence. The GOLM1 expression in prostate cancer cells at the mRNA and protein level was determined by quantitative real-time polymerase chain reaction and Western blot analysis, respectively. A prostate cancer tissue microarray was used to analyze GOLM1 protein expression by immunohistochemistry. RESULTS The immunofluorescence results demonstrated that GOLM1 was located at the cis-Golgi in the DU145 cells. GOLM1 transcripts and protein were overexpressed in a wide variety of prostate cancer cell lines (DU145, 22RV1, PC-3, and LNCaP). Tissue microarray immunohistochemistry demonstrated that GOLM1 protein staining was occasionally found in the normal prostate gland and benign prostatic hyperplasia, whereas that in prostate cancer was predominantly observed in the cytoplasm of tumor cells. GOLM1 protein was strongly expressed in prostate cancer tissues, and there was a significant difference compared with the normal prostate and benign prostatic hyperplasia cases (P < .05). There were no significant differences between GOLM1 overexpression and pathologic variables of prostate cancer, including histologic grade and pathologic stage (P > .05). CONCLUSION Our results suggest that GOLM1 protein is significantly expressed in prostate cancer in comparison with the normal prostate gland and benign prostatic hyperplasia. These findings may suggest that GOLM1 is useful in the diagnosis or therapy of prostate cancer. However, GOLM1 overexpression is not associated with disease stage and grade. UROLOGY 80: 952.e1-952.e7, 2012. (C) 2012 Elsevier Inc.

Li, Z., et al. (2008). "Feasibility of a low-fat/high-fiber diet intervention with soy supplementation in prostate cancer patients after prostatectomy." European Journal of Clinical Nutrition 62(4): 526-536.

Objectives: To evaluate the feasibility and long- term compliance with a low- fat diet supplemented with soy protein in men at increased risk for recurrence after radical prostatectomy. Design: Randomized, control study. Setting: Academic center in USA. Subject: Forty men who had undergone radical prostatectomy and were at increased risk for recurrence. Intervention: Low- fat (15% fat), high- fiber (18 g/ 1000 kcal) diet supplemented with 40 g soy protein isolate (n 26) was compared to USDA recommended diet (n 14). Results: Over 4 years, subjects in the intervention group but not in the control group made and sustained significant changes in their diet as measured by the dietary assessment instruments and urinary isoflavone excretion. In the intervention group, dietary fat intake was reduced from 33.46 +/- 1.27% energy/ day to 21.04 +/- 1.74% (P<0.05), fiber intake increased from 14.6 +/- 1.06 to 21.05 +/- 2.29 g/ day. The insulin growth factor- 1 (IGF- 1) level was decreased from 260.4 +/- 8.6 ng/ ml at baseline to 220.5 +/- 7.9 ng/ ml at 6 months (P<0.05) in the intervention group with no significant change in the control group. An ex vivo assay demonstrated inhibition of LNCaP cell growth (- 20.0 +/- 7.7%, P<0.05) by sera from patients in the intervention group after 6 months of dietary change compared to baseline. Conclusion: These data suggest that long- term low- fat dietary interventions as part of prospective randomized trials in prostate cancer survivors are feasible, and lead to reductions in circulating hormones or other growth factors stimulating prostate cancer growth ex vivo.

Lin, D. W., et al. (2013). "Urinary TMPRSS2:ERG and PCA3 in an Active Surveillance Cohort: Results from a Baseline Analysis in the Canary Prostate Active Surveillance Study." Clinical Cancer Research 19(9): 2442-2450.

Purpose: Active surveillance is used to manage low-risk prostate cancer. Both PCA3 and TMPRSS2:ERG are promising biomarkers that may be associated with aggressive disease. This study examines the correlation of these biomarkers with higher cancer volume and grade determined at the time of biopsy in an active surveillance cohort. Experimental Design: Urine was collected after digital rectal examination prospectively as part of the multi-institutional Canary Prostate Active Surveillance Study (PASS). PCA3 and TMPRSS2:ERG levels were analyzed in urine collected at study entry. Biomarker scores were correlated to clinical and pathologic variables. Results: In 387 men, both PCA3 and TMPRSS2:ERG scores were significantly associated with higher volume disease. For a negative repeat biopsy, and 1% to 10%, 11% to 33%, 34% or more positive cores, median PCA3, and TMPRSS2: ERG scores increased incrementally (P < 0.005). Both PCA3 and TMPRSS2:ERG scores were also significantly associated with the presence of high-grade disease. For a negative repeat biopsy, Gleason 6 and Gleason >= 7 cancers, the median PCA3, and TMPRSS2: ERG scores also increased incrementally (P = 0.02 and P = 0.001, respectively). Using the marker scores as continuous variables, the ORs for a biopsy in which cancer was detected versus a negative repeat biopsy (ref) on modeling was 1.41 (95% CI: 1.07-1.85), P = 0.01 for PCA3 and 1.28 (95% CI: 1.10-1.49), P = 0.001 for TMPRSS2:ERG. Conclusions: For men on active surveillance, both PCA3 and TMPRSS2: ERG seem to stratify the risk of having aggressive cancer as defined by tumor volume or Gleason score. (C) 2013 AACR.

Liu, S., et al. (2010). "Telomerase as an Important Target of Androgen Signaling Blockade for Prostate Cancer Treatment." Molecular Cancer Therapeutics 9(7): 2016-2025.

As the mainstay treatment for advanced prostate cancer, androgen deprivation therapy (ADT) targets the action of androgen receptor (AR) by reducing androgen level and/or by using anti-androgen to compete with androgens for binding to AR. Albeit effective in extending survival, ADT is associated with dose-limiting toxicity and the development of castration-resistant prostate cancer (CRPC) after prolonged use. Because CRPC is lethal and incurable, developing effective strategies to enhance the efficacy of ADT and circumvent resistance becomes an urgent task. Continuous AR signaling constitutes one major mechanism underlying the development of CRPC. The present study showed that methylseleninic acid (MSA), an agent that effectively reduces AR abundance, could enhance the cancer-killing efficacy of the anti-androgen bicalutamide in androgen-dependent and CRPC cells. We found that the combination of MSA and bicalutamide produced a robust downregulation of prostate-specific antigen and a recently identified AR target, telomerase, and its catalytic subunit, human telomerase reverse transcriptase. The downregulation of hTERT occurs mainly at the transcriptional level, and reduced AR occupancy of the promoter contributes to downregulation. Furthermore, apoptosis induction by the two agents is significantly mitigated by the restoration of hTERT. Our findings thus indicate that MSA in combination with anti-androgen could represent a viable approach to improve the therapeutic outcome of ADT. Given the critical role of hTERT/telomerase downregulation in mediating the combination effect and the fact that hTERT/telomerase could be measured in blood and urine, hTERT/telomerase could serve as an ideal tumor-specific biomarker to monitor the efficacy of the combination therapy noninvasively. Mol Cancer Ther; 9(7); 2016-25. (C) 2010 AACR.

Lokhov, P. G., et al. (2010). "Metabolite profiling of blood plasma of patients with prostate cancer." Metabolomics 6(1): 156-163.

Prostate cancer is one of the most common types of cancer in men. It is though extremely important to search for specific markers including metabolites, which concentration in blood could be a diagnostic measure. In this regard, the metabolite profiling of blood plasma was performed with two groups of people: healthy volunteers (n = 30) and patients with prostate cancer, second stage (n = 40). The profiling protocol included proteins removal from blood plasma with methanol and direct analysis of metabolite fractions by mass spectrometry. Identification of the most abundant metabolites in samples was performed using an accurate mass tag and an isotope pattern methods. Cancer-specific metabolites were revealed by statistical analysis of metabolite intensities in the mass spectra. Six different metabolites were found to be cancer-specific. Two metabolites, acylcarnitine and arachidonoyl amine, have the AUC 0.97 and 0.86, respectively, which are higher than those from PSA test, 0.59.

Lopez-Beltran, A., et al. (2009). "Lymphoepithelioma-like carcinoma of the prostate." Human Pathology 40(7): 982-987.

In this report, we summarized the clinicopathologic features of 5 cases of lymphoepithelioma-like carcinoma of the prostate, a rare variant of prostate cancer characterized by a malignant epithelial component densely infiltrated by lymphoid cells. In all 5 patients, there were obstructive symptoms and elevated prostate-specific antigen; one patient had also hematuria. Their ages ranged from 69 to 82 years (mean age, 76 years). The initial diagnosis of lymphoepithelioma-like carcinoma of the prostate was made on transurethral resection in 3 cases and radical prostatectomy in 2 others. In one case the diagnosis of lymphoepithelioma-like carcinoma admixed with conventional acinar adenocarcinoma was an unexpected finding at time of transurethral resection for benign prostatic hyperplasia. Three patients had clinical stage T3 tumors and another had stage T4 disease; stage T1b was present in the remaining case. Microscopically, all tumors contained lymphoepithelioma-like carcinoma, which comprised 10% to 90% of the entire tumor. All cases were associated with adenocarcinoma, either as the sole pattern in 5 cases or with an additional ductal component in 3 cases. One case had additional features of adenosquamous carcinoma. The lymphoepithelioma-like carcinoma component was characterized by indistinct cytoplasmic borders and a syncytial growth pattern. The stroma was densely infiltrated by lymphoid cells admixed with some plasma cells and neutrophils; one case had a prominent infiltration of eosinophils. Immunohistochemical staining demonstrated that lymphoepithelioma-like carcinoma was positive for prostate-specific antigen, prostate acid phosphatase, alpha-methylacyl coenzyme A racemase, and epithelial membrane antigen; several cytokeratins (AE1/AE3, 7, 8, and 20 [rare cells]) were also immunoreactive. The mean Ki-67 labeling index was 53% (range, 40%-70%), and the p53 expression in all cases was low (10%-20%). The lymphoid component was mainly composed of T with a minor subset of B cells, admixed with some dendritic cells and histiocytes as seen by S100 and CD68 immunoreactivity. Latent membrane protein 1 immunostaining and in situ hybridization for Epstein-Barr virus were negative in all 5 lymphoepithelioma-like carcinoma cases. DNA ploidy of lymphoepithelioma-like carcinoma tumors gave DNA histograms with aneuploid peaks. DNA ploidy of the concurrent adenocarcinoma gave DNA aneuploid peaks except in one DNA diploid case. Four patients died of disease from 8 to 26 months; one patient was lost to follow-up. In summary, lymphoepithelioma-like carcinoma of the prostate arise in aggressive prostate cancers at advanced clinical stage. Morphologic recognition and distinction front other prostatic lesions and tumors with prominent lymphoid stroma is critical for its clinical management. (C) 2009 Elsevier Inc. All rights reserved.

Lu, Q., et al. (2009). "Identification of Extracellular delta-Catenin Accumulation for Prostate Cancer Detection." Prostate 69(4): 411-418.
BACKGROUND. Prostate cancer is the second leading cause of cancer death in men, and early detection is essential to reduce mortality and increase survival. delta-Catenin is a unique beta-catenin superfamily protein primarily expressed in the brain but is upregulated in human prostatic adenocarcinomas. Despite its close correlation with the disease, it is unclear whether delta-catenin presents the potential in prostate cancer screening because it is an intracellular protein. In this study, we investigated the hypothesis of delta-catenin accumulation in the urine of prostate cancer patients and its potential pathways of excretion into extracellular milieu. METHODS. Prostate cancer cell cultures, human tissue biopsies, and voided urines were characterized to determine extracellular delta-catenin accumulation and co-isolation with exosomes/prostasomes. RESULTS. We identified delta-catenin in culture media and in the stroma of human prostate cancer tissues. In PC-3 cells in culture, delta-catenin was partially co-localized and co-isolated with raft-associated membrane protein caveolin-1 and glycosylphosphatidylinositol-anchored protein CD59, suggesting its potential excretion into extracellular milieu through exosome/prostasome associated pathways. Interference with endocytic pathway using wortmannin did not block prostasome excretion, but delta-catenin overexpression promoted the extracellular accumulation of caveolin-1. delta-Catenin, caveolin-1, and CD59 were all detected in cell-free human voided urine prostasomes. delta-Catenin immunoreactivity was significantly increased in the urine of prostate cancer patients (P < 0.0005). CONCLUSIONS. This study demonstrated, for the first time, the extracellular accumulation of delta-catenin in urine supporting its potential utility for non-invasive prostate cancer detection. Prostate 69: 411-418, 2009. (C) 2008 Wiley-Liss, Inc.

Lucarelli, G., et al. (2013). "Spondin-2, a Secreted Extracellular Matrix Protein, is a Novel Diagnostic Biomarker for Prostate Cancer." Journal of Urology 190(6): 2271-2277.

Purpose: SPON2 belongs to the F-spondin family of secreted extracellular matrix proteins. It is deregulated in some tumors, including prostate cancer. In this prospective study we assessed the role of serum SPON2 as a biomarker for prostate cancer diagnosis as well as any association between SPON2 levels and clinicopathological features. We also compared the diagnostic performance of this biomarker to that of serum sarcosine, and percent free-to-total and total prostate specific antigen. Materials and Methods: SPON2 was measured using a sandwich enzyme linked immunosorbent assay in serum samples from 286 patients with prostate cancer and 68 with no evidence of malignancy, as confirmed by 10 to 12-core ultrasound guided prostate biopsy. Nonparametric statistical tests and ROC analysis were done to assess the diagnostic performance of SPON2 vs the other biomarkers. Results: Median serum SPON2 was significantly higher in patients with prostate cancer than in those with no evidence of malignancy (77.5 vs 23.6 ng/ml, p <0.0001). ROC analysis showed a higher predictive value of SPON2 (AUC 0.952) than of serum sarcosine (AUC 0.674), percent free-to-total prostate specific antigen (AUC 0.806) and total prostate specific antigen (AUC 0.561). Moreover, patients with low grade prostate cancer had higher median SPON2 levels (p = 0.001). Spearman rank correlation confirmed a negative association with Gleason score (rs = -0.29, p = 0.0005). Conclusions: We found evidence that SPON2 levels were significantly higher in patients with prostate cancer than in healthy individuals. Moreover, this biomarker had better diagnostic performance than serum sarcosine, and percent free-to-total and total prostate specific antigen. This greater accuracy was also present in a subset of patients with normal prostate specific antigen.

Luo, B. and A.-L. Wang (2010). "An update of the markers for prostate cancer." Zhonghua nan ke xue = National journal of andrology 16(6): 531-535.
Prostate cancer is one of the most familiar malignancies in the male urinary system, and its incidence is on the rise in China in recent years. As a most commonly used marker for prostate cancer detection, prostate-specific antigen (PSA) has a high organic but a low carcinomatous specificity, and its clinical application value needs to be reestimated. Many studies have been devoted to the finding of new markers for prostate cancer and some achievements already obtained. This article approaches the markers for prostate cancer in three aspects, DNA, RNA and protein, hoping to offer a new insight into the diagnosis and treatment of prostate cancer.

Maraldo, D., et al. (2007). "Method for quantification of a prostate cancer biomarker in urine without sample preparation." Analytical Chemistry 79(20): 7683-7690.
We describe a macrocantilever-based method for detecting a prostate cancer biomarker (alpha-methylacyl-CoA racemase; AMACR) directly in patient urine without a sample preparation step and without the use of labeled reagents. Clean catch voided urine specimens were prospectively collected from five confirmed prostate cancer patients 3 weeks postbiopsy. The presence of AMACR was measured in a blinded manner by exposing 3 mL of urine to the antiAMACR-immobilized piezoelectric-excited millimeter-sized (PEMC) sensor. The resonance frequency of PEMC decreases as AMACR from sample binds to the antibody on the sensor. The resonance frequency changes for the five patients tested were 4,1314 +/not superset of 35 (n = 2), 269 +/not superset of 17 (n = 2), 977 +/not superset of 64 (n = 3), 600 +/not superset of 31 (n = 2), and 801 +/not superset of 81 (n = 2) Hz, respectively. Positive detection was observed within similar to 15 min. The responses to positive, negative, and buffer controls were -9 +/not superset of 13, -34 +/not superset of 18, and -6 +/not superset of 18 Hz, respectively. Positive verification of AMACR attachment was confirmed by low-pH buffer release. The sensor response was quantitatively related to AMACR concentration in control urine, and the relationship was used in developing an in situ calibration method for quantifying AMACR in patient urine. Estimated concentrations of 42, 2, and 3 fg/mL AMACR were calculated for the three patients' urine, while absence of AMACR was confirmed in control urine (n = 13). Because of simplicity of measurement combined. with high sensitivity and specificity, the method may be a useful adjunct in a point-of-care setting to identify men at increased risk for prostate cancer.

Marcinkiewicz, K., et al. (2012). "The androgen receptor and stem cell pathways in prostate and bladder cancers (Review)." International Journal of Oncology 40(1): 5-12.

Bladder cancer is three times more common in men than in women. However, the physiological basis of the male predominance of bladder cancer remains poorly understood. A higher than expected association of prostate and bladder cancers has also been reported which may indicate a common mechanism of carcinogenesis. Consistent with this, androgens and the androgen receptor (AR) play essential roles in prostate carcinogenesis and are believed to play a role in bladder carcinogenesis. There is also evidence implicating cancer stem cells in prostate and bladder cancers. Indeed putative prostate and bladder cancer stem cells share some common molecular features. We highlight key proteins (CD49f, CD133, PTEN, CD44) which are implicated in both prostate and bladder cancers and are enriched in putative prostate and bladder cancer stem cells. We examine published chromatin immuno-precipitation studies analyzing the genome-wide distribution of the AR to identify AR association with, and by inference potential AR-regulation of, these loci. We discuss recent evidence indicating a role for the AR in the splicing of the key urological stem cell protein CD44. We propose a model whereby aberrant AR regulation of these putative stem cell proteins contributes to malignant transformation of prostate and bladder cells. For these reasons we propose that the relationship between androgens and cancer stem cell associated proteins warrants further investigation.

Margel, D., et al. (2014). "Personalized prostate cancer screening among men with high risk genetic predisposition- study protocol for a prospective cohort study." Bmc Cancer 14.

Background: Prostate cancer screening among the general population is highly debatable. Nevertheless, screening among high-risk groups is appealing. Prior data suggests that men carrying mutations in the BRCA1&2 genes may be at increased risk of developing prostate cancer. Additionally, they appear to develop prostate cancer at a younger age and with a more aggressive course. However, prior studies did not systematically perform prostate biopsies and thus cannot determine the true prevalence of prostate cancer in this population. Methods: This will be a prospective diagnostic trial of screening for prostate cancer among men with genetic predisposition. The target population is males (40-70 year old) carrying a BRCA1 and/or BRCA2 germ line mutation. They will be identified via our Genetic counseling unit. All men after signing an informed consent will undergo the following tests: PSA, free to total PSA, MRI of prostate and prostate biopsy. The primary endpoint will be to estimate the prevalence, stage and grade of prostate cancer in this population. Additionally, the study aims to estimate the impact of these germ line mutations on benign prostatic hyperplasia. Furthermore, this study aims to create a bio-bank of tissue, urine and serum of this unique cohort for future investigations. Finally, this study will identify an inception cohort for future interventional studies of primary and secondary prevention. Discussion: The proposed research is highly translational and focuses not only on the clinical results, but on the future specimens that will be used to advance our understanding of prostate cancer patho-physiology. Most importantly, these high-risk germ-line mutation carriers are ideal candidates for primary and secondary prevention initiatives.

Marszall, M. P., et al. (2015). "Engrailed-2 protein as a potential urinary prostate cancer biomarker: a comparison study before and after digital rectal examination." European Journal of Cancer Prevention 24(1): 51-56.

This study was designed to compare and evaluate the presence of engrailed-2 (EN2) protein in urine collected before and after prostate massage as a diagnostic marker for prostate cancer (PCa). We analysed and compared 76 urine samples (38 before and 38 after prostate massage) from the benign group (BPH) and 66 urine samples (33 before and 33 after prostate massage) from patients with PCa confirmed by prostate biopsy. EN2 levels from the PCa and men with BPH (age range 50-82) were related to the tumour stage, Gleason score and prostate-specific antigen. EN2 levels were determined by enzyme-linked immunosorbent assay in urine. The median EN2 levels in urine after prostate massage were significantly different from those determined in urine before prostate massage (1.25ng/ml in the PCa group and 0.34ng/ml in the BPH). The mean EN2 levels in PCa patients were 3.76-fold higher than those in non-PCa patients after prostate massage. The distinct influence of prostate massage on EN2 levels was found to be related to the Gleason score and tumour stage. EN2 may be considered a marker of PCa with certain limitations, such as those related to tumour staging. The specificity and sensitivity of the protocol are highly dependent on prostate massage. (C) 2014 Wolters Kluwer Health vertical bar Lippincott Williams & Wilkins.

Martens-Uzunova, E. S., et al. (2014). "Long Noncoding RNA in Prostate, Bladder, and Kidney Cancer." European Urology 65(6): 1140-1151.

Context: Genomic regions without protein-coding potential give rise to millions of protein-noncoding RNA transcripts (noncoding RNA) that participate in virtually all cellular processes. Research over the last 10 yr has accumulated evidence that long noncoding RNAs (lncRNAs) are often altered in human urologic cancers. Objective: To review current progress in the biology and implication of lncRNAs associated with prostate, bladder, and kidney cancer. Evidence acquisition: The PubMed database was searched for articles in the English language with combinations of the Medical Subject Headings terms long non coding RNA, long noncoding RNA, long untranslated RNA, cancer, neoplasms, prostate, bladder, and kidney. Evidence synthesis: We summarise existing knowledge on the systematics, biology, and function of lncRNAs, particularly these involved in prostate, kidney, and bladder cancer. We also discuss the possible utilisation of lncRNAs as novel biomarkers and potential therapeutic targets in urologic malignancies and portray the major challenges and future perspectives of ongoing lncRNA research. Conclusions: LncRNAs are important regulators of gene expression interacting with the major pathways of cell growth, proliferation, differentiation, and survival. Alterations in the function of lncRNAs promote tumour formation, progression, and metastasis of prostate, bladder, and kidney cancer. LncRNAs can be used as noninvasive tumour markers in urologic malignancies. Increased knowledge of the molecular mechanisms by which lncRNAs perform their function in the normal and malignant cell will lead to a better understanding of tumour biology and could provide novel therapeutic targets for the treatment of urologic cancers. Patient summary: In this paper we reviewed current knowledge of long noncoding RNAs (lncRNAs) for the detection and treatment of urologic cancers. We conclude that lncRNAs can be used as novel biomarkers in prostate, kidney, or bladder cancer. LncRNAs hold promise as future therapeutic targets, but more research is needed to gain a better understanding of their biologic function. (C) 2013 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Martinez-Pineiro, L., et al. (2014). "Evaluation of urinary prostate cancer antigen-3 (PCA3) and TMPRSS2-ERG score changes when starting androgen-deprivation therapy with triptorelin 6-month formulation in patients with locally advanced and metastatic prostate cancer." Bju International 114(4): 608-616.

Objective To assess prostate cancer antigen-3 (PCA3) and TMPRSS2-ERG scores in patients with advanced and metastatic prostate cancer at baseline and after 6 months of treatment with triptorelin 22.5 mg, and analyse these scores in patient-groups defined by different disease characteristics. Patients and Methods The Triptocare study was a prospective, open-label, multicentre, single-arm, Phase III study of triptorelin 22.5 mg in men with locally advanced or metastatic prostate cancer, who were naive to androgen-deprivation therapy (ADT). The primary objective was to model the urinary PCA3 change at 6 months, according to baseline variables. Other outcome measures included urinary PCA3 and TMPRSS2-ERG scores and statuses, and serum testosterone and prostate-specific antigen (PSA) levels at baseline and at 1, 3 and 6 months after initiation of ADT. Safety was assessed by recording adverse events and changes in laboratory parameters. Results The intent-to-treat population comprised 322 patients; 39 (12.1%) had non-assessable PCA3 scores at baseline, and 109/322 (33.9%), 215/313 (68.7%) and 232/298 (77.9%) had non-assessable PCA3 scores at 1, 3 and 6 months, respectively. Baseline Gleason score was the only variable associated with non-assessability of PCA3 score at 6 months (P = 0.017) the hazard of having a non-assessable PCA3 score at 6 months was 1.821-fold higher (95% confidence interval 1.186-2.805) in patients with a Gleason score vs those with a Gleason score <= 6. The median PCA3 scores at baseline were significantly higher in patients aged 65 years vs those aged <65 years and in patients with a serum PSA level <100 ng/mL vs those with serum PSA level of >200 ng/mL. The median PCA3 score was significantly lower in patients with metastasis than in patients with no metastasis or unknown metastasis status. TMPRSS2-ERG scores 35 were considered positive (n = 149 l51.6%D. Age, presence of metastasis, PSA level and Gleason score at baseline were not associated with a significant difference in the proportion of TMPRSS2-ERG-positive scores. The median serum PSA levels decreased from 45.5 ng/mt, at baseline to 1.2 ng/mL after 6 months, and as expected, >90% of patients achieved castrate levels of testosterone (<50 ng/dL) at 1, 3, and 6 months during triptorelin treatment. The safety profile reported from this study is consistent with the known safety profile of triptorelin. Conclusion These data from the Trip tocare study suggest that urinary PCA3 or TMPRSS2-ERG score are not reliable markers of cancer stage in advanced prostate cancer. Urinary PCA3 and TMPRSS2-ERG scores do not appear to be useful in assessing response to ADT in advanced prostate cancer, with most patients having non-assessable scores after 6 months of treatment.

Masters, J. R. (2011). "Prostate Cancer Proteomics." Omics-a Journal of Integrative Biology 15(3): 169-171.

Proteomics has offered the hope of biomarker discovery to improve the management of prostate cancer. Markers are needed for screening and diagnosis, distinguishing latent from aggressive disease, defining the men who will benefit from therapy, differentiating localized from metastatic disease, predicting outcome and identifying new targets for therapy. There are many potential sources of proteins derived from the prostate, including urine, prostatic fluid (expressed or ejaculate), serum, and plasma or tissue, each with distinct advantages and limitations. Equally, there are many methodological platforms for proteomic studies of the prostate. Despite the promise, protoemics has yielded little of relevance to the management of prostate cancer, and most of the work that has been published is either irreproducible or of no clinical value.

Mazzola, C. R. E., et al. (2011). "Emerging biomarkers for the diagnosis, staging and prognosis of prostate cancer." Progres En Urologie 21(1): 1-10.

The introduction and widespread adoption of prostate-specific antigen (PSA) has revolutionized the way prostate cancer is diagnosed and treated. However, the use of PSA has also led to overdiagnosis and overtreatment of prostate cancer resulting in controversy about its use for screening. PSA also has limited predictive accuracy for predicting outcomes after treatment and for making clinical decisions about adjuvant and salvage therapies. Hence, there is an urgent need for novel biomarkers to supplement PSA for detection and management of prostate cancer. A plethora of promising blood- and urine-based biomarkers have shown promise in early studies and are at various stages of development (Human kallikrein 2, Early Prostate Cancer Antigen, Transforming Growth Factor-Beta 1 and Interleukin-6, Endoglin, PCA3, AMACR and ETS Gene Fusions). In this article, we review those biomarkers and then discuss the challenges a biomarker has to undergo before it is approved in a clinical use. (C) 2010 Elsevier Masson SAS. All rights reserved.

Mazzucchelli, R., et al. (2009). "IMMUNOHISTOCHEMICAL EXPRESSION OF PROSTATE STEM CELL ANTIGEN IN CYSTOPROSTATECTOMIES WITH INCIDENTAL PROSTATE CANCER." International Journal of Immunopathology and Pharmacology 22(3): 755-762.

High expression of Prostate Stem Cell Antigen (PSCA) has been shown to be associated with adverse prognostic features in clinically-diagnosed prostate cancer. The aim of this study is to analyze PSCA expression in cystoprostatectomies with incidental prostate carcinoma (PCa). PSCA expression was evaluated immunohistochemically in normal-looking epithelium (NEp), high-grade prostatic intraepithelial neoplasia (HGPIN) and pT2a Gleason score 6 acinar adenocarcinoma. The evaluation was carried out on 20 cystoprostatectomies (CyPs) with incidental PCa from men with bladder urothelial carcinoma (UC), and 20 radical prostatectomies (RPs) with hormonally untreated PCa from men with clinically detected PCa. Ki-67 was also investigated. The percentages of PSCA positive cells in HGPIN were significantly higher than in NEp (NEp: CyP, mean 2.92% +/- standard deviation 6.26%; R-P, 3.5% +/- 6.46%. HGPIN: CyP, 13.67% +/- 12.78%; RP, 14.67% +/- 11.34%) (p<0.001). The proportions of positive cells in PCa were greater than in HGPIN (CyP, 20.25% +/- 15.96%; RP, 22.58% +/- 13.67%) (p<0.001). For Ki-67 labeling, the proportions of positive nuclei in the CyPs significantly increased from NEp through HGPIN to PCa. A similar trend was seen in the RPs. In the CyPs the percentages of PSCA and Ki67 positive cells were lower than in the RPs, the differences between the CyP and RP compartments being not statistically significant. Our findings suggest that PSCA is a marker associated with neoplastic transformation of prostate cells, both in CyPs and RPs. However, there are no significant differences between CyPs with incidental prostate carcinoma and RPs with clinically diagnosed cancer.

McGrath, S. E., et al. (2013). "EN2: a novel prostate cancer biomarker." Biomarkers in Medicine 7(6): 893-901.

Extensive efforts to identify a clinically useful biomarker for the diagnosis of prostate cancer have resulted in important insights into the biology of the disease, but no new test has been approved by regulatory authorities. The unmet need has also shifted to identifying biomarkers that not only diagnose prostate cancer but also indicate whether the patient has significant' disease. EN2 is a homeobox-containing transcription factor secreted specifically by prostate cancers into urine, where it can be detected by a simple ELISA assay. A number of studies have demonstrated the enormous potential of EN2 to address this unmet need and provide the urologist with a simple, cheap and efficient prostate cancer biomarker.

McLerran, D., et al. (2008). "Analytical validation of serum proteomic profiling for diagnosis of prostate cancer: Sources of sample bias." Clinical Chemistry 54(1): 44-52.

BACKGROUND: This report and a companion report describe a validation of the ability of serum proteomic profiling via SELDI-TOF mass spectrometry to detect prostatic cancer. Details of this 3-stage process have been described. This report describes the development of the algorithm and results of the blinded test for stage 1. METHODS: We derived the decision algorithm used in this study from the analysis of serum samples from patients with prostate cancer (n = 181) and benign prostatic hyperplasia (BPH) (n 143) and normal controls (n = 220). We also derived a validation test set from a separate, geographically diverse set of serum samples from 42 prostate cancer patients and 42 controls without prostate cancer. Aliquots were subjected to randomization and blinded analysis, and data from each laboratory site were subjected to the decision algorithm and decoded. RESULTS: Using the data collected from the validation test set, the decision algorithm was unsuccessful in separating cancer from controls with any predictive utility. Analysis of the experimental data revealed potential sources of bias. CONCLUSION: The ability of the decision algorithm to successfully differentiate between prostate cancer, BPH, and control samples using data derived from serum protein profiling was compromised by bias. (c) 2007 American Association for Clinical Chemistry.

Michel, M. C. and W. Vrydag (2006). "alpha(1)-, alpha(2)- and beta-adrenoceptors in the urinary bladder, urethra and prostate." British Journal of Pharmacology 147: S88-S119.

1 We have systematically reviewed the presence, functional responses and regulation of alpha(1)-, alpha(2)- and beta-adrenoceptors in the bladder, urethra and prostate, with special emphasis on human tissues and receptor subtypes. 2 alpha(1)-Adrenoceptors are only poorly expressed and play a limited functional role in the detrusor. alpha(1)-Adrenoceptors, particularly their alpha(1A)-Subtype, show a more pronounced expression and promote contraction of the bladder neck, urethra and prostate to enhance bladder outlet resistance, particularly in elderly men with enlarged prostates. alpha(1)-Adrenoceptor agonists are important in the treatment of symptoms of benign prostatic hyperplasia, but their beneficial effects may involve receptors within and outside the prostate. 3 alpha(2)-Adrenoceptors, mainly their alpha(2A)-subtype, are expressed in bladder, urethra and prostate. They mediate pre-junctional inhibition of neurotransmitter release and also a weak contractile effect in the urethra of some species, but not humans. Their overall post-junctional function in the lower urinary tract remains largely unclear. 4 beta-Adrenoceptors mediate relaxation of smooth muscle in the bladder, urethra and prostate. The available tools have limited the unequivocal identification of receptor subtypes at the protein and functional levels, but it appears that the beta(3)- and beta(2)-subtypes are important in the human bladder and urethra, respectively. beta(3)-Adrenoceptor agonists are promising drug candidates for the treatment of the overactive bladder. 5 We propose that the overall function of adrenoceptors in the lower urinary tract is to promote urinary continence. Further elucidation of the functional roles of their subtypes will help a better understanding of voiding dysfunction and its treatment.

Mittal, R. D., et al. (2012). "Base excision repair pathway genes polymorphism in prostate and bladder cancer risk in North Indian population." Mechanisms of Ageing and Development 133(4): 127-132.

Purpose: Carcinogens causes DNA damage, including oxidative lesions that are removed efficiently by the base excision repair (BER) pathway. Variations in BER genes may reduce DNA repair capacity, leading to development of urological cancers. Methods: This study included 195 prostate cancer (PCa) and 212 bladder cancer (BC) patients and 250 controls who had been frequency matched by age, sex, and ethnicity. We genotyped XRCC1 Exon 6 (C > T), 9 (G > A), 10 (G > A), OGG1 Exon 7 (C > G) and APE1 Exon 5 (T > G) genes polymorphism using PCR-RFLP and ARMS. Results: GA of XRCC1 Exon 9 demonstrated increased risk with PCa as well as in BC (p = 0.001; p = 0.006). Similarly variant containing genotype revealed association with PCa (p = 0.031). Haplotype of XRCC1 also associated with significant risk for PCa and BC. The APE1 GG genotype showed a decreased risk of BC (OR = 0.25; p = 0.017). Variant genotype GG of OGG1 demonstrated significant risk with BC (p = 0.028). Conclusions: Our observations suggested increased risk for PCa and BC in case of GA genotype for XRCC1, and variant GG in case of OGG1. However APE1 GG genotype conferred a protective association with BC susceptibility. Larger studies and the more SNPs in the same pathway are needed to verify these findings. (C) 2011 Elsevier Ireland Ltd. All rights reserved.

M'Koma, A. E., et al. (2007). "Detection of pre-neoplastic and neoplastic prostate disease by MADI profiling of urine." Biochemical and Biophysical Research Communications 353(3): 829-834.

The heterogeneous progression to the development of prostate cancer (PCa) has precluded effective early detection screens. Existing prostate cancer screening paradigms have relatively poor specificity for cancer relative to other prostate diseases, commonly benign prostatic hyperplasia (BPH). A method for discrimination of BPH, HGPIN, and PCa urine proteome was developed through testing 407 patient samples using matrix assisted laser desorption-mass spectrometry time of flight (MALDI-TOF). Urine samples were adsorbed to reverse phase resin, washed, and the eluant spotted directly for MALDI-TOF analysis of peptides. The processing resolved over 130 verifiable signals of a mass range of 1000-5000 m/z to suggest 71.2% specificity and 67.4% sensitivity in discriminating PCa vs. BPH. Comparing BPH and HGPIN resulted in 73.6% specificity and 69.2% sensitivity. Comparing PCa and HGPIN resulted in 80.8% specificity and 81.0% sensitivity. The high throughput, low-cost assay method developed is amenable for large patient numbers required for supporting biomarker identification. (c) 2006 Elsevier Inc. All rights reserved.

Moad, M., et al. (2013). "A Novel Model of Urinary Tract Differentiation, Tissue Regeneration, and Disease: Reprogramming Human Prostate and Bladder Cells into Induced Pluripotent Stem Cells." European Urology 64(5): 753-761.

Background: Primary culture and animal and cell-line models of prostate and bladder development have limitations in describing human biology, and novel strategies that describe the full spectrum of differentiation from foetal through to ageing tissue are required. Recent advances in biology demonstrate that direct reprogramming of somatic cells into pluripotent embryonic stem cell (ESC)-like cells is possible. These cells, termed induced pluripotent stem cells (iPSCs), could theoretically generate adult prostate and bladder tissue, providing an alternative strategy to study differentiation. Objective: To generate human iPSCs derived from normal, ageing, human prostate (Pro-iPSC), and urinary tract (UT-iPSC) tissue and to assess their capacity for lineage-directed differentiation. Design, setting, and participants: Prostate and urinary tract stroma were transduced with POU class 5 homeobox 1 (POU5F1; formerly OCT4), SRY (sex determining region Y)-box 2 (SOX2), Kruppel-like factor 4 (gut) (KLF4), and v-myc myelocytomatosis viral oncogene homolog (avian) (MYC, formerly C-MYC) genes to generate iPSCs. Outcome measurements and statistical analysis: The potential for differentiation into prostate and bladder lineages was compared with classical skin-derived iPSCs. The student t test was used. Results and limitations: Successful reprogramming of prostate tissue into Pro-iPSCs and bladder and ureter into UT-iPSCs was demonstrated by characteristic ESC morphology, marker expression, and functional pluripotency in generating all three germ-layer lineages. In contrast to conventional skin-derived iPSCs, Pro-iPSCs showed a vastly increased ability to generate prostate epithelial-specific differentiation, as characterised by androgen receptor and prostate-specific antigen induction. Similarly, UT-iPSCs were shown to be more efficient than skin-derived iPSCs in undergoing bladder differentiation as demonstrated by expression of urothelial-specific markers: uroplakins, claudins, and cytokeratin; and stromal smooth muscle markers: alpha-smooth-muscle actin, calponin, and desmin. These disparities are likely to represent epigenetic differences between individual iPSC lines and highlight the importance of organ-specific iPSCs for tissue-specific studies. Conclusions: IPSCs provide an exciting new model to characterise mechanisms regulating prostate and bladder differentiation and to develop novel approaches to disease modelling. Regeneration of bladder cells also provides an exceptional opportunity for translational tissue engineering. (C) 2013 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Mondul, A. M., et al. (2012). "Serum Vitamin D and Risk of Bladder Cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial." Cancer Epidemiology Biomarkers & Prevention 21(7): 1222-1225.

Background: The one previous prospective study of vitamin D status and risk of urinary bladder cancer found that male smokers with low serum 25-hydroxy-vitamin D[25(OH)D] were at a nearly two-fold increased risk. We conducted an analysis of serum 25(OH)D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study and examined whether serum vitamin D binding protein (DBP) concentration confounded or modified the association. Methods: Three hundred and seventy-five cases of bladder cancer were matched 1:1 with controls based on age (+/- 5 years), race, sex, and date of blood collection (+/- 30 days). Conditional logistic regression was used to estimate ORs and 95% confidence intervals (CI) of bladder cancer by prediagnosis levels of 25(OH)D. Results: We found no strong or statistically significant association between serum 25(OH)D and bladder cancer risk (Q1 vs. Q4: OR, 0.84; 95% CI, 0.52-1.36; P-trend = 0.56). Further adjustment for, or stratification by, serum DBP did not alter the findings, nor was there a main effect association between DBP and risk. Conclusion: In contrast to an earlier report, we observed no association between vitamin D status and risk of bladder cancer; this difference could be due to the inclusion of women and nonsmokers in the current study population or due to the differences in the distribution of vitamin D concentrations between the two study populations. Impact: These findings may contribute to future meta-analyses and help elucidate whether the vitamin D bladder cancer association varies across populations. Cancer Epidemiol Biomarkers Prey; 21(7); 1222-5. (C) 2012 AACR.

Morgan, R., et al. (2011). "Engrailed-2 (EN2): A Tumor Specific Urinary Biomarker for the Early Diagnosis of Prostate Cancer." Clinical Cancer Research 17(5): 1090-1098.

Purpose: Prostate cancer (PC) is the second most common cause of cancer related death in men. A number of key limitations with prostate specific antigen (PSA), currently the standard detection test, has justified evaluation of new biomarkers. We have assessed the diagnostic potential of Engrailed-2 (EN2) protein, a homeodomain-containing transcription factor expressed in PC cell lines and secreted into the urine by PC in men. Experimental Design: EN2 expression in PC cell lines and prostate cancer tissue was determined by semi-quantative RT-PCR and immunohistochemistry. First pass urine [without prior digital rectal examination (DRE)] was collected from men presenting with urinary symptoms (referred to exclude/confirm the presence of prostate cancer) and from controls. EN2 protein was measured by ELISA in urine from men with PC (n = 82) and controls (n = 102). Results: EN2 was expressed and secreted by PC cell lines and PC tissue but not by normal prostate tissue or stroma. The presence of EN2 in urine was highly predictive of PC, with a sensitivity of 66% and a specificity of 88.2%, without requirement for DRE. There was no correlation with PSA levels. These results were confirmed independently by a second academic center. Conclusions: Urinary EN2 is a highly specific and sensitive candidate biomarker of prostate cancer. A larger multicenter study to further evaluate the diagnostic potential of EN2 is justified. Clin Cancer Res; 17(5); 1090-8. (C)2011 AACR.

Morrissey, J. J., et al. (2015). "Urine Aquaporin 1 and Perilipin 2 Differentiate Renal Carcinomas From Other Imaged Renal Masses and Bladder and Prostate Cancer." Mayo Clinic Proceedings 90(1): 35-42.

Objective: To evaluate the sensitivity and specificity of urine aquaporin 1 (AQP1) and perilipin 2 (PLIN2) concentrations to diagnose clear cell or papillary renal cell carcinoma (RCC) by comparing urine concentrations of these unique biomarkers in patients with RCC, noncancer renal masses, bladder cancer, and prostate cancer. Methods: From February 1, 2012, through October 31, 2012, preoperative urine samples were obtained from patients with a presumptive diagnosis of RCC based on an imaged renal mass, prostate cancer, or transitional cell bladder cancer. Imaged renal masses were diagnosed postnephrectomy-as malignant or benign-by histology. Urine AQP1 and PLIN2 concentrations were measured by using a sensitive and specific Western blot and normalized to urine creatinine concentration. Results: Median concentrations of urine AQP1 and PLIN2 in patients with clear cell and papillary RCC (n=47) were 29 and 36 relative absorbance units/mg urine creatinine, respectively. In contrast, median concentrations in patients with bladder cancer (n=22) and prostate cancer (n=27), patients with chromophobe tumors (n=7), and patients with benign renal oncocytomas (n=9) and angiomyolipomas (n=7) were all less than 10 relative absorbance units/mg urine creatinine (Kruskal-Wallis test, P<.001 vs RCC for both biomarkers) and comparable with those in healthy controls. The area under the receiver operating characteristic curve ranged from 0.99 to 1.00 for both biomarkers. Conclusion: These results support the specificity and sensitivity of urine AQP1 and PLIN2 concentrations for RCC. These novel tumor-specific proteins have high clinical validity and high potential as specific screening biomarkers for clear cell and papillary RCC as well as in the differential diagnosis of imaged renal masses.

Mottet, N., et al. (2008). "Highlights on prostate cancer from urological and oncological congresses in 2007." European Urology Supplements 7(6): 460-476.

Objective: This paper communicates the major new findings on prostate cancer (PCa) that were presented at the 2007 annual meetings of the European Association of Urology (EAU), American Urological Association (AUA), and American Society of Clinical Oncology (ASCO) and discussed during a closed meeting in September 2007. Recent Findings: Sonoelastography-targeted biopsy may be an alternative to systematic biopsy for decreasing the number of biopsy cores. Twelve cores appear to be optimal for a systematic biopsy. Discontinuing aspirin before a biopsy is not mandatory. In patients with poor-risk PCa, long-term, adjuvant androgen-deprivation therapy (ADT) to radiotherapy is recommended. Patients with a prostate-specific antigen doubling time (PSADT) > 12 mo, <= 50% positive biopsy cores, a biopsy Gleason score <= 7, and previous low-dose rate brachytherapy are at increased risk of an organ-confined relapse of PCa and may be treated with salvage radical prostatectomy. Patients with T04N0-2M0 PCa who are not suitable for local treatment and have a PSA > 50 ng/ml and/or a PSADT <= 12 mo should receive immediate ADT. Toremifene citrate may increase bone mineral density in men receiving ADT. An elevated C-reactive protein level may be a predictor of poor survival in hormone-refractory PCa patients receiving docetaxel-based therapy. Conclusion: It can be concluded that many interesting new data on PCa were presented at the 2007 oncological and urological congresses, some of which may have an impact on clinical practice, whereas other data raise new questions that will have to be answered by further research. (C) 2008 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Mueller, H., et al. (2008). "Evaluation of serum and urinary myeloid related protein-14 as a marker for early detection of prostate cancer." Journal of Urology 180(4): 1309-1312.

Purpose: Early detection of prostate cancer by prostate specific antigen testing is subject to ongoing controversy. Thus, practical tests to improve or replace prostate specific antigen would be highly desirable. In diagnostic studies promising results were shown for myeloid related protein-14 in serum and urine. However, confirmation in longitudinal population based studies is needed. Materials and Methods: Incident prostate cancer cases (32) and controls (74) matched by age were identified during a 2-year followup of a longitudinal study. The group of cases was further complemented by a sample of 24 prostate cancer cases recruited before initiation of treatment from a clinical study. A commercially available test was used to analyze serum and urinary myeloid related protein-14 in blinded fashion. Results: In contrast to prostate specific antigen, serum and urinary myeloid related protein-14 could not significantly discriminate between prostate cancer cases and controls. Conclusions: In our study, neither serum nor urinary myeloid related protein-14 proved suitable to distinguish prostate cancer cases from controls. Overall myeloid related protein-14 performed much worse than prostate specific antigen and it does not seem useful to reduce false-positive findings of prostate specific antigen in the controversial range of 4 to 10 ng/ml.

Nakayama, K., et al. (2014). "The C-Terminal Fragment of Prostate-Specific Antigen, a 2331 Da Peptide, as a New Urinary Pathognomonic Biomarker Candidate for Diagnosing Prostate Cancer." PloS one 9(9).

Background and Objectives: Prostate cancer (PCa) is one of the most common cancers and leading cause of cancer-related deaths in men. Mass screening has been carried out since the 1990s using prostate-specific antigen (PSA) levels in the serum as a PCa biomarker. However, although PSA is an excellent organ-specific marker, it is not a cancer-specific marker. Therefore, the aim of this study was to discover new biomarkers for the diagnosis of PCa. Materials and Methods: We focused on urine samples voided following prostate massage (digital rectal examination [DRE]) and conducted a peptidomic analysis of these samples using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MSn). Urinary biomaterials were concentrated and desalted using CM-Sepharose prior to the following analyses being performed by MALDI-TOF/MSn: 1) differential analyses of mass spectra; 2) determination of amino acid sequences; and 3) quantitative analyses using a stable isotope-labeled internal standard. Results: Multivariate analysis of the MALDI-TOF/MS mass spectra of urinary extracts revealed a 2331 Da peptide in urine samples following DRE. This peptide was identified as a C-terminal PSA fragment composed of 19 amino acid residues. Moreover, quantitative analysis of the relationship between isotope-labeled synthetic and intact peptides using MALDI-TOF/MS revealed that this peptide may be a new pathognomonic biomarker candidate that can differentiate PCa patients from non-cancer subjects. Conclusion: The results of the present study indicate that the 2331 Da peptide fragment of PSA may become a new pathognomonic biomarker for the diagnosis of PCa. A further large-scale investigation is currently underway to assess the possibility of using this peptide in the early detection of PCa.

Nejatollahi, F., et al. (2013). "Antiproliferative and apoptotic effects of a specific antiprostate stem cell single chain antibody on human prostate cancer cells." Journal of oncology 2013: 839831-839831.

Prostate stem cell antigen (PSCA) is a highly glycosylated cell surface protein which is overexpressed in several malignancies including prostate, pancreas, and urinary bladder cancers. Tumor suppression has been reported by anti-PSCA antibody. Small and high affinity single chain antibodies (scFv) have been introduced as effective agents for cancer immunotargeting approaches. In the present study, we used a phage antibody display library of scFv and selected two antibodies against two immunodominant epitopes of PSCA by panning process. The reactivity of the scFvs for the corresponding epitopes was determined by phage ELISA. The binding specificity of antibodies to PSCA-expressing prostate cancer cell line, DU-145, was analyzed by flow cytometry. The antiproliferative and apoptotic induction effects were evaluated by MTT and Annexin-V assays, respectively. Results represented functional scFv C5-II which could bind specifically to DU-145 cells and significantly inhibited the proliferation of these cells (61%) with no effect on PSCA-negative cells. The antibody also induced apoptosis in the PSCA expressing cells. The percentage of the apoptotic cells after 24hrs of exposure to 500scFv/cell was 33.80%. These results demonstrate that the functional anti-PSCA scFv C5-II has the potential to be considered as a new agent for targeted therapy of prostate cancer.

Neuhaus, J., et al. (2013). "Seminal Plasma as a Source of Prostate Cancer Peptide Biomarker Candidates for Detection of Indolent and Advanced Disease." PloS one 8(6).

Background: Extensive prostate specific antigen screening for prostate cancer generates a high number of unnecessary biopsies and over-treatment due to insufficient differentiation between indolent and aggressive tumours. We hypothesized that seminal plasma is a robust source of novel prostate cancer (PCa) biomarkers with the potential to improve primary diagnosis of and to distinguish advanced from indolent disease. Methodology/Principal Findings: In an open-label case/control study 125 patients (70 PCa, 21 benign prostate hyperplasia, 25 chronic prostatitis, 9 healthy controls) were enrolled in 3 centres. Biomarker panels a) for PCa diagnosis (comparison of PCa patients versus benign controls) and b) for advanced disease (comparison of patients with post surgery Gleason score <7 versus Gleason score >7) were sought. Independent cohorts were used for proteomic biomarker discovery and testing the performance of the identified biomarker profiles. Seminal plasma was profiled using capillary electrophoresis mass spectrometry. Pre-analytical stability and analytical precision of the proteome analysis were determined. Support vector machine learning was used for classification. Stepwise application of two biomarker signatures with 21 and 5 biomarkers provided 83% sensitivity and 67% specificity for PCa detection in a test set of samples. A panel of 11 biomarkers for advanced disease discriminated between patients with Gleason score 7 and organ-confined (<pT3a) or advanced (>= pT3a) disease with 80% sensitivity and 82% specificity in a preliminary validation setting. Seminal profiles showed excellent pre-analytical stability. Eight biomarkers were identified as fragments of N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase, prostatic acid phosphatase, stabilin-2, GTPase IMAP family member 6, semenogelin-1 and -2. Restricted sample size was the major limitation of the study. Conclusions/Significance: Seminal plasma represents a robust source of potential peptide makers for primary PCa diagnosis. Our findings warrant further prospective validation to confirm the diagnostic potential of identified seminal biomarker candidates.

Nguyen, P.-N., et al. (2011). "A Panel of TMPRSS2:ERG Fusion Transcript Markers for Urine-Based Prostate Cancer Detection with High Specificity and Sensitivity." European Urology 59(3): 407-414.

Background: The TMPRSS2:ERG fusion is both prevalent and unique to prostate cancer (PCa) and has great potential for noninvasive diagnosis of PCa in bodily fluids. Objectives: To evaluate the specificity and sensitivity of the TMPRSS2: ERG fusion in urine from diverse clinical contexts and to explore potential clinical applications. Design, setting, and participants: A total of 101 subjects were enrolled in 2008 from urologic oncology clinics to form three study groups: 44 PCa free, 46 confirmed PCa, and 11 negative prostate biopsies. The PCa-free group included females, healthy young men, and post-radical prostatectomy (RP) patients. The confirmed PCa group was composed of patients under active surveillance, scheduled for treatment, or with metastatic disease. Measurements: Urine was collected after attentive digital rectal exam (DRE) and coded to blind group allocation for laboratory test. RNA from urine sediments was analyzed using a panel of four TMPRSS2: ERG fusion markers with quantitative polymerase chain reaction (qPCR). Results and limitations: Our fusion markers demonstrated very high technical specificity and sensitivity for detecting a single fusion-positive cancer cell (VCaP) in the presence of at least 3000 cells in urine sediments. In clinical analysis, there were no fusion-positive samples in the PCa-free group (0 of 44 samples), while there were 16 of 46 (34.8%) fusion-positive samples in the confirmed PCa group. The fusion incidence varied significantly among the three PCa subgroups. The clinical sensitivity increased to 45.4% in cancer patients prior to treatments. The fusion markers were detected in 2 of 11 (18.2%) biopsy-negative patients, suggesting potentially false negative biopsies. This study is not prospective and is limited in sample sizes. Conclusions: Our novel panel of TMPRSS2: ERG fusion markers provided a very specific and sensitive tool for urine-based detection of PCa. Theses markers can potentially be used to diagnose patients with PCa who have negative biopsies. (C) 2010 European Association of Urology. Published by Elsevier B. V. All rights reserved.

Nilsson, J., et al. (2009). "Prostate cancer-derived urine exosomes: a novel approach to biomarkers for prostate cancer." British Journal of Cancer 100(10): 1603-1607.

Herein, we describe a novel approach in the search for prostate cancer biomarkers, which relies on the transcriptome within tumour exosomes. As a proof-of-concept, we show the presence of two known prostate cancer biomarkers, PCA-3 and TMPRSS2: ERG the in exosomes isolated from urine of patients, showing the potential for diagnosis and monitoring cancer patients status. British Journal of Cancer (2009) 100, 1603-1607. doi: 10.1038/sj.bjc.6605058 www.bjcancer.com Published online 28 April 2009 (C) 2009 Cancer Research UK

Nna, E. (2013). "The end of the road for prostate specific antigen testing." Nigerian Journal of Clinical Practice 16(4): 407-417.

Many candidate biomarkers for diagnosis of prostate cancer have been investigated, but prostate-specific antigen (PSA) testing remains the frontline test for both mass screening and individual clinical testing. Although the PSA test is cost-effective, analytically reliable, and flexibly high throughput, it has a very weak correlation with prostate malignancy. This has resulted in over-diagnosis and over-treatment of patients leading to costly economic, social, and psychological impacts. PSA testing lacks the ability to molecularly characterize prostate diseases and define aggressiveness and lethality, which are necessary to influence choice of treatment. Therefore, newer molecular tests are beginning to replace the PSA tests. The prostate cancer antigen 3 test has shown superiority and is now widely used. The recently reported sarcosine urine test, the already delineated TMPRSS2: ETS fusion genes, the glutathione-S-transferase P1 serum marker, and enhancer of zeste homolog 2 biomarker may also help improve diagnosis and prognostication of prostate cancer. The analytical trend is toward a multiplex testing format using molecular and/or proteomic techniques that are reliable, accurate, reproducible, and ensure rapid quantitation. Therefore, validation of these newer biomarkers and their assays are necessary for both large-scale clinical trials and clinical utility.

Nna, E., et al. (2010). "Endogenous Control Genes in Prostate Cells: Evaluation of Gene Expression Using 'Real-Time' Quantitative Polymerase Chain Reaction." Medical Principles and Practice 19(6): 433-439.

Objective: Our aims were to measure the level of expression of Abelson (ABL1), beta-glucuronidase (GUS) and glucose-6-phosphate dehydrogenase (G6PD) genes in exfoliated urine cells from healthy and transrectal ultrasound biopsy patients with elevated prostate-specific antigen levels and/or abnormal digital rectal examinations or urinary symptoms indicative of prostate problems, as well as in archived formalin-fixed paraffin-embedded prostate materials. Materials and Methods: Real-time quantitative polymerase chain reaction (RQ-PCR) was used to evaluate the suitability of the 3 control genes, i.e. ABL1, GUS and G6PD, as control genes for prostate cancer cells. Exfoliated urine cells from 30 healthy males, 53 male patients, 138 cases of archived paraffin-embedded prostate tissues and 3 prostate cell lines were sampled. All cells were lysed in guanidine isothiocyanate buffer from which RNA was extracted and converted to cDNA by random hexamer priming. RQ-PCR was performed using TaqMan chemistries. Results: There was no significant difference in the level of expression for each of the 3 control genes in the cell lines. There was a significant difference in GUS transcript level between patients and healthy controls in both urine and prostate tissue sections ($p < 0.05$). G6PD transcript numbers also differed significantly from those of GUS in the prostate cell lines and tissue sections ($p < 0.05$). The transcript numbers of all the control genes were significantly reduced in aged samples ($p < 0.001$). Conclusion: The ABL1 gene was the most stable control gene in both clinical specimens and cell lines. Therefore, we recommend its use to enable standardization and interlaboratory comparisons for the RQ-PCR of prostatic tumour markers. Copyright (C) 2010 S. Karger AG, Basel

Nomura, T., et al. (2012). "Efficacy of prophylactic single-dose therapy using fluoroquinolone for prostate brachytherapy." Japanese Journal of Radiology 30(4): 317-322.

There is little definitive evidence to guide the use of prophylactic antibiotics for prostate brachytherapy. The purpose of this study is to evaluate the incidence of postimplant infections in patients who receive antimicrobial prophylaxis with pazufloxacin (PZFX). A total of 84 patients who underwent prostate brachytherapy received a single intravenous dose of PZFX at 500 mg perioperatively for 1 day. No postimplant antibiotic medication was prescribed. Urinalysis, plasma white blood cell (WBC) count, and C reactive protein (CRP) levels were evaluated before the implantation, on the day after implantation, and on the 7th and 28th days after brachytherapy. None of the 84 patients (0.0%) developed a symptomatic urinary tract infection or had febrile infectious complications after brachytherapy. There were statistically significant elevations in the levels of erythrocytes, leukocytes, bacteria in urine, plasma WBC and CRP postoperatively, but these values did not exceed the normal range or were only slightly elevated on the day after brachytherapy (day 1) and on day 7. All laboratory examinations had returned to the normal range on day 28. Single-dose therapy with fluoroquinolone helps to prevent infections after prostate brachytherapy.

Nyalwidhe, J. O., et al. (2013). "Increased bisecting N-acetylglucosamine and decreased branched chain glycans of N-linked glycoproteins in expressed prostatic secretions associated with prostate cancer progression." Proteomics Clinical Applications 7(9-10): 677-689.

PurposeUsing prostatic fluids rich in glycoproteins like prostate-specific antigen and prostatic acid phosphatase (PAP), the goal of this study was to identify the structural types and relative abundance of glycans associated with prostate cancer status for subsequent use in emerging MS-based glycopeptide analysis platforms. Experimental designA series of pooled samples of expressed prostatic secretions (EPS) and exosomes reflecting different stages of prostate cancer disease were used for N-linked glycan profiling by three complementary methods, MALDI-TOF profiling, normal-phase HPLC separation, and triple quadropole MS analysis of PAP glycopeptides. ResultsGlycan profiling of N-linked glycans from different EPS fluids indicated a global decrease in larger branched tri- and tetra-antennary glycans. Differential exoglycosidase treatments indicated a substantial increase in bisecting N-acetylglucosamines correlated with disease severity. A triple quadrupole MS analysis of the N-linked glycopeptides sites from PAP in aggressive prostate cancer pools was done to cross-reference with the glycan profiling data. Conclusion and clinical relevanceChanges in glycosylation as detected in EPS fluids reflect the clinical status of prostate cancer. Defining these molecular signatures at the glycopeptide level in individual samples could improve current approaches of diagnosis and prognosis.

Oberpenning, F., et al. (2008). "DiaPat urine test for prostate cancer. Predictive value for results of transrectal ultrasound-guided prostate biopsies." Urologe 47(6): 735-739.

Background. A novel urine test for early detection of prostate cancer (PCA), distributed and marketed by the company DiaPat, is advertised by the statement "correct analysis in 9 of 10 cases." Patients and methods. The test separates urinary polypeptides by means of capillary electrophoresis and characterizes the peptides in a time-of-flight mass spectrometer. The DiaPat test was performed on the urine of 18 men prior to multiple ultrasound-guided prostate biopsies. Results. Sixteen of the 18 samples met the requirements for sample quality as established by the manufacturer. Eight of these 16 urine samples had been collected from patients in whom biopsies consecutively detected PCA; the remaining eight patients had benign biopsy results. Among the eight patients with detected PCA, the urine test yielded a low probability for PCA in three cases and a high probability in five. Within the group of eight patients with benign biopsy results, the urine test predicted a high probability for PCA in five men and a low probability in three. For the given PCA incidence of 50% within the investigated population, the DiaPat test correctly predicted biopsy results in one half of the population, whereas prediction in the remaining half was incorrect. Conclusion. Unless reliable validation of the DiaPat urine test for PCA is available, no clinical consequences should be drawn from the test results.

Okamoto, A., et al. (2009). "Protein profiling of post-prostatic massage urine specimens by surface-enhanced laser desorption/ionization time-of-flight mass spectrometry to discriminate between prostate cancer and benign lesions." Oncology Reports 21(1): 73-79.

Post-prostatic massage urine specimens (PMUS) are expected to be rich in proteins originating from the prostatic acini. In this study, we created a PMUS bank consisting of 57 samples obtained from patients with biopsy-proven prostate cancer (PC) and 56 samples from subjects with biopsy-proven benign lesions to analyze protein profiles of PMUS by surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS), Strong anion-exchange (Q10), weak cation-exchange (CM10) and immobilized metal affinity capture (IMAC30) ProteinChip Arrays were used for protein profiling. In PC samples, single-marker analysis detected 49 mass peaks that were significantly up-regulated and 23 peaks that were significantly down-regulated, compared with peaks obtained from benign lesion samples. To confirm reproducibility we performed additional three rounds of assay using CM10 chip with pH 4.0 binding buffer. Among these significant peaks, a peak of m/z 10788 was significant throughout all 4 rounds of assays. For hierarchical clustering analysis (HCA), we used the 72 peaks which revealed significant differences in single-marker analysis. The heat map discriminated PC from benign lesions with a sensitivity of 91.7% and a specificity of 83.3%. Therefore, SELDI-TOF MS profiling of PMUS can be applied to differentiate patients with PC from cancer-free subjects. However, further investigation is required to verify the usefulness of this method in clinical practice.

O'Kane, H. F., et al. (2006). "Targeting death receptors in bladder, prostate and renal cancer." Journal of Urology 175(2): 432-438.

Purpose: We describe key components of normal and aberrant death receptor pathways, the association of these abnormalities with tumorigenesis in bladder, prostate and renal cancer, and their potential application in novel therapeutic strategies targeted toward patients with cancer. Materials and Methods: A MEDLINE literature search of the key words death receptors, TRAIL (tumor necrosis factor related apoptosis inducing ligand), FAS, bladder, prostate, renal and cancer was done to obtain information for review. A brief overview of the TRAIL and FAS death receptor pathways, and their relationship to apoptosis is described. Mechanisms that lead to nonfunction of these pathways and how they may contribute to tumorigenesis are linked. Current efforts to target death receptor pathways as a therapeutic strategy are highlighted. Results: Activation of tumor cell expressing death receptors by cytotoxic immune cells is the main mechanism by which the immune system eliminates malignant cells. Death receptor triggering induces a caspase cascade, leading to tumor cell apoptosis. Receptor gene mutation or hypermethylation, decoy receptor or splice variant over expression, and downstream inhibitor interference are examples of the ways that normal pathway functioning is lost in cancers of the bladder and prostate. Targeting death receptors directly through synthetic ligand administration and blocking downstream inhibitor molecules with siRNA or antisense oligonucleotides represent novel therapeutic strategies under development. Conclusions: Research into the death receptor pathways has demonstrated the key role that pathway aberrations have in the initiation and progression of malignancies of the bladder, prostate and kidney. This new understanding has resulted in exciting approaches to restore the functionality of these pathways as a novel therapeutic strategy.

Olsson, A. Y., et al. (2007). "Role of E2F3 expression in modulating cellular proliferation rate in human bladder and prostate cancer cells." Oncogene 26(7): 1028-1037.

cation and overexpression of the E2F3 gene at 6p22 in human bladder cancer is associated with increased tumour stage, grade and proliferation index, and in prostate cancer E2F3 overexpression is linked to tumour aggressiveness. We first used small interfering RNA technology to confirm the potential importance of E2F3 overexpression in bladder cancer development. Knockdown of E2F3 expression in bladder cells containing the 6p22 amplicon strongly reduced the extent of bromodeoxyuridine (BrdU) incorporation and the rate of cellular proliferation. In contrast, knockdown of CDKAL1/FLJ20342, another proposed oncogene, from this amplicon had no effect. Expression cDNA microarray analysis on bladder cancer cells following E2F3 knockdown was then used to identify genes regulated by E2F3, leading to the identification of known E2F3 targets such as Cyclin A and CDC2 and novel targets including pituitary tumour transforming gene 1, Polo-like kinase 1 (PLK1) and Caveolin-2. For both bladder and prostate cancer, we have proposed that E2F3 protein overexpression may cooperate with removal of the E2F inhibitor retinoblastoma tumor suppressor protein (pRB) to drive cellular proliferation. In support of this model, we found that ectopic expression of E2F3a enhanced the BrdU incorporation, a marker of cellular proliferation rate, of prostate cancer DU145 cells, which lack pRB, but had no effect on the proliferation rate of PC3 prostate cancer cells that express wild-type pRB. BrdU incorporation in PC3 cells could, however, be increased by overexpressing E2F3a in cells depleted of pRB. When taken together, these observations indicate that E2F3 levels have a critical role in modifying cellular proliferation rate in human bladder and prostate cancer.

Osunkoya, A. O. and J. I. Epstein (2007). "Primary mucin-producing urothelial-type adenocarcinoma of prostate: report of 15 cases." The American journal of surgical pathology 31(9): 1323-1329.

Prostatic urothelial-type adenocarcinoma arises through a process of glandular metaplasia of the prostatic urethral urothelium and subsequent in situ adenocarcinoma sometimes associated with villous adenoma. These prostatic adenocarcinomas are analogous to nonurachal adenocarcinomas arising in the bladder from cystitis glandularis. Only 2 cases of urothelial-type adenocarcinoma from an institution other than our own have been previously described. The distinction between adenocarcinoma from another organ secondarily involving the prostate, usual adenocarcinoma of the prostate, and prostatic urothelial-type adenocarcinoma can present a significant diagnostic challenge and has significant therapeutic implications. Fifteen cases of prostatic urothelial-type adenocarcinoma were retrieved from the consult files of one of the authors. Mean patient age at diagnosis was 72 years (range 58 to 93 y). All men had negative colonoscopies, clinically excluding a colonic primary. Bladder primaries were ruled out clinically or pathologically in radical resection specimens. Follow-up was available on all men with a mean of 50.3 months (range 2 to 161 mo). All men presented with urinary obstruction symptoms with 3 (20%) also having mucusuria and 2 (13.3%) also having hematuria. Four men (26.7%) developed metastatic disease and 8 (53.3%) died of disease. In 8/15 (53%) cases, glandular metaplasia of the prostatic urethra and contiguous transition to adenocarcinoma were identified. Multiple histologic patterns were observed including dissection of the stroma by mucin pools 15/15 (100%), villous features 7/15 (47%), necrosis 2/15 (13.3%), signet ring cells 3/15 (20%), perineural invasion 1/15 (6.7%), focal squamous differentiation 1/15 (6.7%), and a granulomatous inflammatory response 1/15 (6.7%). Immunohistochemical stains were negative for prostate specific antigen, prostate specific acid phosphatase, CDX2, and beta-catenin in all cases. Stains were positive for high molecular weight cytokeratin in 12/12 cases (100%), and CK7 and CK20 in 10/12 cases (83.3%). Prostatic urothelial-type adenocarcinoma is a rare aggressive cancer arising in the prostate. The differential diagnosis includes conventional prostatic mucinous adenocarcinoma and secondary infiltration from a colonic or bladder adenocarcinoma. Immunohistochemistry for prostate specific antigen, prostate specific acid phosphatase, and high molecular weight cytokeratin along with morphology can help rule out conventional prostate carcinoma. beta-catenin, CDX2, and clinical studies are needed to rule out colonic adenocarcinoma. As prostatic urothelial-type adenocarcinoma is entirely analogous to bladder adenocarcinoma in both, its morphology and immunophenotype, only clinical studies or in some cases pathologic examination of the cystoprostatectomy specimen can exclude infiltration from a primary bladder adenocarcinoma.

Pace, G., et al. (2010). "Sarcoma of prostate: case report and review of the literature." Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica / Associazione ricerche in urologia 82(2): 105-108.
OBJECTIVES: Prostate sarcomas are rare entity, the most common is leiomyosarcoma which account for 0.1% of all prostate malignancies. The presenting symptoms are mainly obstructive urinary symptoms. Surgery with chemo- or radiotherapy are the mainstay treatment options. The overall survival rate remains poor regardless of initial tumour size, grade or histological subtype. Immunohistochemistry reveals tumour cells diffusely positive for vimentin, smooth muscle actin, focally positive for progesterone receptor, whilst keratins are usually negative. MATERIALS AND METHODS: We describe a case of a patient affected by sarcoma of prostate. Furthermore, we reviewed the cases of prostate sarcomas available in literature to clarify the best therapeutic options to be applied. RESULTS: In the case described leiomyosarcoma diagnosed by an ultrasound guided biopsy was characterized by fascicles of spindle-shaped cells with a variable degree of nuclear atypia. The immunohistochemistry showed positive staining for smooth muscle actin, vimentin and focally for the S-100 protein. The patient was treated with radical retropubic prostatectomy and radiotherapy of the local recurrence, and chemotherapy at metastases onset. CONCLUSIONS: Prostate sarcomas are highly aggressive, with limited therapeutic options. An early diagnosis and complete surgical excision with negative margins offer patients the long-term disease free survival.

Pandha, H., et al. (2012). "Urinary engrailed-2 (EN2) levels predict tumour volume in men undergoing radical prostatectomy for prostate cancer." Bju International 110(6B): E287-E292.

What's known on the subject? and What does the study add? There are a lot of potential prostate cancer biomarkers being evaluated. All aim to improve on the sensitivity and specificity of PSA. EN2 was recently shown by our group to have better sensitivity and specificity than PSA. EN2 is a simple ELISA test and is not dependent on other parameters, even PSA, unlike all the other current biomarkers under evaluation. To date, no marker correlates with the amount of cancer present - the present study shows this positive correlation with EN2 in men undergoing prostatectomy. The potential utility of this work is that by knowing that the level of EN2 corresponds to the amount of cancer present, irrelevant of tumour grade and number of cancer foci, we can define an EN2 level corresponding to small cancers, which can then undergo surveillance. We are conducting a further study that is aimed at determining whether the levels of EN2 in urine can indicate 'significant' vs 'non-significant cancer' using the threshold of 0.5 mL cancer (after Epstein's work). OBJECTIVES To evaluate the relationship between levels of a recently described prostate cancer biomarker engrailed-2 (EN2) in urine and cancer volume in men who had undergone radical prostatectomy (RP) for prostate cancer. To date, prostate-specific antigen (PSA) levels have not reliably predicted prostate cancer volume. Reliable volume indicator biomarker(s) may aid management decisions, e. g. active treatment vs active surveillance. PATIENTS AND METHODS Archived patient samples from the Aarhus Prostate Cancer Project, Denmark, were assessed. Pre-treatment mid-stream urines, without preceding prostatic massage, were collected and stored at -80 degrees C. Urinary EN2 levels were measured by a recently published enzyme-linked immunosorbent assay. RESULTS In all, 88 of the whole cohort of 125 men (70%) were positive for EN2 in their urine (> 42.5 g/L); 38/58 (65%) men where cancer volume data was available. There was no statistical relationship between urinary EN2 levels and serum PSA levels. PSA levels did not correlate with tumour stage, combined Gleason grade, total prostatic weight or cancer volume. There was a strong statistical relationship between urinary EN2 and prostate cancer volume by linear regression (P = 0.006). Higher EN2 levels correlated with tumour stage T1 vs T2 (P = 0.027). CONCLUSIONS Pre-surgical urinary EN2 levels were associated with increasing tumour stage and closely reflected the volume of cancer in RP specimens. Given the ease of collection (no prostatic massage required) and the simplicity, low cost and robustness of the assay, EN2 may become a useful biomarker in not only identifying which patients have prostate cancer but may also facilitate risk stratification by indicating the burden of tumour volume.

Park, H. S., et al. (2014). "Synergistic Antitumor Effect of NVP-BEZ235 and Sunitinib on Docetaxel-resistant Human Castration-resistant Prostate Cancer Cells." Anticancer Research 34(7): 3457-3468.

According to recent studies, mTOR (mammalian target of rapamycin) inhibitor and tyrosine kinase inhibitor (TKI) can be used as combinational agents to enhance the antitumor effect or overcome resistance to one of the agents. In the present study, we investigated the synergistic interaction between NVP-BEZ235, a PI3K (phosphoinositide 3-kinase)/mTOR dual inhibitor, and sunitinib, a TKI, in castration-resistant prostate cancer (CRPC) cells with docetaxel resistance. Prostate cancer cells with different sensitivities to hormones and docetaxel levels were exposed to escalating doses of NVP-BEZ235 alone and in combination with sunitinib. The synergy between NVP-BEZ235 and sunitinib was determined by the combination index, three-dimensional model, and clonogenic assays. Flow cytometry and western blot analysis of proteins related to apoptosis and cell survival axis were performed. The combination of NVP-BEZ235 and sunitinib caused a significant synergistic antitumor effect over a wide range of doses in docetaxel-resistant CRPC cells. Furthermore, the IC50 (half-maximal inhibitory concentration) of NVP-BEZ235 and sunitinib was reduced by 7.8-fold and 6.6-fold, respectively. The three-dimensional synergy analysis resulted in a synergy volume of 182.47 mu M/ml(2)%, indicating a strong synergistic effect of combination therapy. Combination therapy caused an induction of caspase-dependent apoptosis in docetaxel-resistant CRPC cells. Adding sunitinib did not produce any additional effect on the NVP-BEZ235-mediated inhibition of PI3K/AKT/mTOR phosphorylation. In conclusion, combining NVP-BEZ235, a dual PI3K/mTOR inhibitor, with sunitinib can synergistically potentiate the antitumor effect in CRPC cells after docetaxel failure though induction of caspase-dependent apoptosis.

Pascal, L. E., et al. (2009). "Gene expression down-regulation in CD90(+) prostate tumor-associated stromal cells involves potential organ-specific genes." Bmc Cancer 9.

Background: The prostate stroma is a key mediator of epithelial differentiation and development, and potentially plays a role in the initiation and progression of prostate cancer. The tumor-associated stroma is marked by increased expression of CD90/THYI. Isolation and characterization of these stromal cells could provide valuable insight into the biology of the tumor microenvironment. Methods: Prostate CD90(+) stromal fibromuscular cells from tumor specimens were isolated by cell-sorting and analyzed by DNA microarray. Dataset analysis was used to compare gene expression between histologically normal and tumor-associated stromal cells. For comparison, stromal cells were also isolated and analyzed from the urinary bladder. Results: The tumor-associated stromal cells were found to have decreased expression of genes involved in smooth muscle differentiation, and those detected in prostate but not bladder. Other differential expression between the stromal cell types included that of the CXC-chemokine genes. Conclusion: CD90(+) prostate tumor-associated stromal cells differed from their normal counterpart in expression of multiple genes, some of which are potentially involved in organ development.

Perk, J., et al. (2006). "Reassessment of Id1 protein expression in human mammary, prostate, and bladder cancers using a monospecific rabbit monoclonal anti-Id1 antibody." Cancer Research 66(22): 10870-10877.

Id proteins are a class of dominant-negative antagonists of helix-loop-helix transcription factors and have been shown to control differentiation of a variety of cell types in diverse organisms. Although the importance of Id1 in tumor endothelial cells is well established, the expression and role of the Id1 protein in human cancer cells is controversial. To explore this issue, we developed and characterized a highly specific rabbit monoclonal antibody against Id1 to assess its expression in human breast, prostate, and bladder malignancies. Our results show that in usual types of human mammary carcinomas, the Id1 protein is expressed exclusively in the endothelium. Interestingly, we detected nuclear expression of the Id1 protein in the tumor cells in 10 of 45 cases of poorly differentiated and highly aggressive carcinoma with metaplastic morphology. Similarly, only 1 of 30 prostate cancer samples showed Id1-positive tumor cells, whereas in almost all, endothelial cells showed high Id1 expression. Intriguingly, whereas normal prostate glands do not show any Id1 protein expression, basal layer cells of benign prostate glands in proximity to tumors expressed high levels of the Id1 protein. In contrast to the lack of Id1 expression in the usual types of mammary and prostate cancers, the majority of transitional cell bladder tumors showed Id1 protein expression in both tumor and endothelial cells. These results suggest that further refinement of Id1 expression patterns in a variety of tumor types will be necessary to identify and study the functional roles played by Id1 in human neoplastic processes.

Pflueger, D., et al. (2009). "N-myc Downstream Regulated Gene 1 (NDRG1) Is Fused to ERG in Prostate Cancer." Neoplasia 11(8): 804-U113.

A step toward the molecular classification of prostate cancer was the discovery of recurrent erythroblast transformation specific rearrangements, most commonly fusing the androgen-regulated TMPRSS2 promoter to ERG. The TMPRSS2-ERG fusion is observed in around 90% of tumors that overexpress the oncogene ERG. The goal of the current study was to complete the characterization of these ERG-overexpressing prostate cancers. Using fluorescence in situ hybridization and reverse transcription-polymerase chain reaction assays, we screened 101 prostate cancers, identifying 34 cases (34%) with the TMPRSS2-ERG fusion. Seven cases demonstrated ERG rearrangement by fluorescence in situ hybridization without the presence of TMPRSS2-ERG fusion messenger RNA transcripts. Screening for known 5' partners, we determined that three cases harbored the SLC45A3-ERG fusion. To discover novel 5' partners in these ERG-overexpressing and ERG-rearranged cases, we used paired-end RNA sequencing. We first confirmed the utility of this approach by identifying the TMPRSS2-ERG fusion in a known positive prostate cancer case and then discovered a novel fusion involving the androgen-inducible tumor suppressor, NDRG1 (N-myc downstream regulated gene 1), and ERG in two cases. Unlike TMPRSS2-ERG and SCL45A3-ERG fusions, the NDRG1-ERG fusion is predicted to encode a chimeric protein. Like TMPRSS2, SCL45A3 and NDRG1 are inducible not only by androgen but also by estrogen. This study demonstrates that most ERG-overexpressing prostate cancers harbor hormonally regulated TMPRSS2-ERG, SLC45A3-ERG, or NDRG1-ERG fusions. Broader implications of this study support the use of RNA sequencing to discover novel cancer translocations.

Phillips, R. (2014). "Prostate cancer: urinary glycoprofile identifies presence and grade of cancer." Nature reviews. Urology 11(12): 664-664.

Phuong-Nhi, B., et al. (2013). "TMPRSS2-ERG Fusion Transcripts in Matched Urine and Needle Rinse Material after Biopsy for the Detection of Prostate Cancer." Clinical Chemistry 59(1): 245-251.

BACKGROUND: Current methods for detecting TMPRSS2-ERG fusion transcript in the urine of patients with suspected prostate cancer lack diagnostic sensitivity. We combined urine and prostate biopsy rinse material (BRM) assays to improve the fusion gene detection rate. METHODS: Eighty patients with clinical and/or prostate-specific antigen suspicion of prostate cancer were prospectively included in the study. Urine samples were collected before and after prostate biopsy, and BRM was collected from the biopsy needle. We used reverse-transcription PCR (RT-PCR) for the detection of fusion transcripts. Microfocal cancer (MFC) on biopsy was defined by a single core involved with <= 3 mm of cancer with Gleason score 3 + 3. We statistically assessed the association between RT-PCR and biopsy results. RESULTS: Urine alone, BRM alone, and both samples were obtained in 4, 19, and 57 patients, respectively. Three patients were excluded because of insufficient material. In the remaining 77 patients, cancer was detected on biopsy in 42 (55%). The diagnostic sensitivity of the assay for cancer detection was 62% (95% CI 47%-78%), 69% (53%-85%), and 89% (73%-99%) with BRM alone, urine alone, and paired samples, respectively. The lowest values were obtained with the urine assay in patients with MFC or Gleason score >3 + 3 cancer. Assays of paired samples provided increased diagnostic sensitivity in all subgroups of patients. CONCLUSIONS: TMPRSS2-ERG fusion gene detection may be improved by performing assays in both urine and BRM. Insufficient cell numbers in urine samples and cell lysis during centrifugation may explain the low diagnostic sensitivity of the urine assay. (C) 2012 American Association for Clinical Chemistry

Pin, E., et al. (2013). "The role of proteomics in prostate cancer research: Biomarker discovery and validation." Clinical Biochemistry 46(6): 524-538.

Purpose: Prostate Cancer (PCa) represents the second most frequent type of tumor in men worldwide. Incidence increases with patient age and represents the most important risk factor. PCa is mostly characterized by indolence, however in a small percentage of cases (3%) the disease progresses to a metastatic state. To date, the most important issue concerning PCa research is the difficulty in distinguishing indolent from aggressive disease. This problem frequently results in low-grade PCa patient overtreatment and, in parallel; an effective treatment for distant and aggressive disease is not yet available. Result: Proteomics represents a promising approach for the discovery of new biomarkers able to improve the management of PCa patients. Markers more specific and sensitive than PSA are needed for PCa diagnosis, prognosis and response to treatment. Moreover, proteomics could represent an important tool to identify new molecular targets for PCa tailored therapy. Several possible PCa biomarkers sources, each with advantages and limitations, are under investigation, including tissues, urine, serum, plasma and prostatic fluids. Innovative high-throughput proteomic platforms are now identifying and quantifying new specific and sensitive biomarkers for PCa detection, stratification and treatment. Nevertheless, many putative biomarkers are still far from being applied in clinical practice. Conclusions: This review aims to discuss the recent advances in PCa proteomics, emphasizing biomarker discovery and their application to clinical utility for diagnosis and patient stratification. (C) 2012 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Ploussard, G. and A. de la Taille (2010). "Urine biomarkers in prostate cancer." Nature Reviews Urology 7(2): 101-109.

The deficiencies of serum PSA as a prostate-cancer-specific diagnostic test are well recognized. Thus, the development of novel biomarkers for prostate cancer detection remains an important and exciting challenge. Noninvasive urine-based tests are particularly attractive candidates for large-scale screening protocols, and biomarker discovery programs using urine samples have emerged for detecting and predicting aggressiveness of prostate cancer. Some new biomarkers already outperform serum PSA in the diagnosis of this disease. Currently, the PCA3 (prostate cancer antigen 3) urine test is probably the best adjunct to serum PSA for predicting biopsy outcome, and has proven its clinical relevance by surpassing the predictive abilities of traditional serum biomarkers. New research methods are also emerging, and high-throughput technologies will facilitate high-dimensional biomarker discovery. Future approaches will probably integrate proteomic, transcriptomic and multiplex approaches to detect novel biomarkers, and aim to identify combinations of multiple biomarkers to optimize the detection of prostate cancer. In addition, an unmet need remains for markers that differentiate indolent from aggressive cancers, to better inform treatment decisions.

Prager, A. J., et al. (2013). "Urinary aHGF, IGFBP3 and OPN as diagnostic and prognostic biomarkers for prostate cancer." Biomarkers in Medicine 7(6): 831-841.

Aim: Serum PSA screening for prostate cancer (PCa) is controversial. Here, we identify three urinary biomarkers - aHGF, IGFBP3 and OPN - for PCa screening and prognostication. Methods: Urinary aHGF, OPN and IGFBP3 from healthy men (n = 19) and men with localized (n = 65) and metastatic (n = 36) PCa were quantified via ELISA. Mann-Whitney nonparametric t-test and the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) analyses were used to analyze associations. Results: Mean aHGF and IGFBP3 levels were significantly elevated in PCa patients versus controls (p = 0.0006 and p = 0.0012, respectively), and the area under the curve of the receiver operating characteristic curve (indicator of diagnostic accuracy) for aHGF and IGFBP3 was 0.75 and 0.74, respectively. OPN levels were significantly higher in metastatic groups (p = 0.0060) versus localized and controls (area under the curve = 0.68). Conclusion: Urinary aHGF and IGFBP3 exhibit the capacity for diagnostic discrimination for PCa, whereas OPN may indicate presence of metastatic disease.

Principe, S., et al. (2012). "Identification of Prostate-Enriched Proteins by In-depth Proteomic Analyses of Expressed Prostatic Secretions in Urine." Journal of Proteome Research 11(4): 2386-2396.

Urinary expressed prostatic secretion or "EPS-urine" is proximal tissue fluid that is collected after a digital rectal exam (DRE). EPS-urine is a rich source of prostate-derived proteins that can be used for biomarker discovery for prostate cancer (PCa) and other prostatic diseases. We previously conducted a comprehensive proteome analysis of direct expressed prostatic secretions (EPS). In the current study, we defined the proteome of EPS-urine employing Multidimensional Protein Identification Technology (MudPIT) and providing a comprehensive catalogue of this body fluid for future biomarker studies. We identified 1022 unique proteins in a heterogeneous cohort of 11 EPS-urines derived from biopsy negative noncancer diagnoses with some benign prostatic diseases (BPH) and low-grade PCa, representative of secreted prostate and immune system-derived proteins in a urine background. We further applied MudPIT-based proteomics to generate and compare the differential proteome from a subset of pooled urines (pre-DRE) and EPS-urines (post-DRE) from noncancer and PCa patients. The direct proteomic comparison of these highly controlled patient sample pools enabled us to define a list of prostate-enriched proteins detectable in EPS-urine and distinguishable from a complex urine protein background. A combinatorial analysis of both proteomics data sets and systematic integration with publicly available proteomics data of related body fluids, human tissue transcriptomic data, and immunohistochemistry images from the Human Protein Atlas database allowed us to demarcate a robust panel of 49 prostate-derived proteins in EPS-urine. Finally, we validated the expression of seven of these proteins using Western blotting, supporting the likelihood that they originate from the prostate. The definition of these prostatic proteins in EPS-urine samples provides a reference for future investigations for prostatic-disease biomarker studies.

Protopsaltis, I., et al. (2013). "Linking Pre-Diabetes with Benign Prostate Hyperplasia. IGFBP-3: A Conductor of Benign Prostate Hyperplasia Development Orchestra?" PloS one 8(12).

Benign prostatic hyperplasia (BPH) represents a pattern of non-malignant growth of prostatic fibromuscular stroma. Metabolic disturbances such us pre-diabetes and metabolic syndrome may have a role in BPH pathophysiology. A potential explanation for the above relationship involves the insulin-like growth factor (IGF) axis as well as IGF binding proteins, (IGFBPs) of which the most abundant form is IGFBP-3. Therefore, the aim of the present study was to investigate the association between intra-prostatic levels of IGF-1, IGF-2 as well as to evaluate the role of locally expressed IGFBP-3 in BPH development in pre-diabetes. A total of 49 patients admitted to the Urology department of a tertiary urban Greek hospital, for transurethral prostate resection, or prostatectomy and with pre-diabetes [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) or both] were finally included. The majority of the sample consisted of subjects with IGT (51.0%), followed by IFG and IGT (32.7%) and isolated IFG (16.3%). For all participants a clinical examination was performed and blood samples were collected. In addition, total prostate (TP) volume or transitional zone (TZ) volume were estimated by transrectal ultrasonography. The results of the multivariate analysis regarding TP volume showed that higher PSA ($p<0.001$), larger waist circumference ($p=0.007$) and higher IGFBP-3 expression levels ($p<0.001$) independently predicted higher TP volume. The results regarding the volume of the TZ showed that higher PSA ($p<0.001$), larger waist circumference ($p<0.001$) and higher IGFBP-3 expression levels ($p=0.024$) were independently associated with higher TZ volume. Our findings show that intra-prostatic levels of IGFBP-3, PSA and waist circumference, but not overall obesity, are positively associated with prostate volume. IGFBP-3 seems to be a multifunctional protein, which can potentiate or inhibit IGF activity.

Provenzano, M. (2012). "New biomarkers in prostate cancer." Praxis 101(2): 115-121.

Prostate cancer (PCa) is one of the most common solid cancers and one of the most important causes of morbidity and mortality worldwide in men. So far, several efforts have been devoted to identify prostate cancer biomarkers, which allow a discrimination between indolent and clinically significant diseases, however with scarce results. The prostate-specific antigen (PSA) still remains the marker of choice for PCa diagnosis, prognosis, and active surveillance. Thus, a sensitive and specific independent indicator, easy to screen in blood or urine is still not available. This review will provide a new insight into the role of previous (i.e. PSA) and new biomarkers, to use separately or in combination for prostate cancer screening and early detection programs.

Rajpar, S. and K. Fizazi (2013). "Bone Targeted Therapies in Metastatic Castration-Resistant Prostate Cancer." Cancer Journal 19(1): 66-70.

Prostate cancer is the most common male cancer. About 90% of metastatic patients will develop bone metastases. Bone disease is responsible of pain, deterioration of quality of life and serious bone complications. Proliferation of prostate cancer cells in the bone marrow induces osteoclast activation and osteolysis. Targeting the bone micro-environment reduces morbidity. Relevant preclinical and clinical studies of bone-targeted therapies in castration-resistant prostate cancer were identified in PubMed and clinical trial databases. Different drugs are available or in development that target bone resorption (bisphosphonates, RANK ligand inhibitors), bone formation (endothelin 1 inhibitors), cancer cell migration (SRC-family kinase inhibitors, vascular endothelial growth factor-MET inhibitors), and survival (radiopharmaceuticals). In phase III trials, zoledronic acid, denosumab, and radium-223 were shown to significantly delay skeletal-related events. Radium-223 was also shown to improve overall survival. Biomarkers of bone resorption (urinary N-telopeptide) and bone making (alkaline phosphatase) have an independent prognostic impact. Targeting the bone microenvironment is an important component of castration-resistant prostate cancer management to reduce bone complications and improve overall survival. Biomarkers of bone turnover have an independent prognostic impact.

Reynolds, M. A., et al. (2007). "Molecular markers for prostate cancer." Cancer Letters 249(1): 5-13.

Serum PSA testing has been used for over 20 years as an aid in the diagnosis and management of prostate cancer. Although highly sensitive, it suffers from a lack of specificity, showing elevated serum levels in a variety of other conditions including prostatitis, benign prostate hyperplasia, and non-cancerous neoplasia. During this period, numerous serum protein analytes have been investigated as alternative and/or supplemental tests for PSA, however in general these analytes have likewise suffered from a lack of specificity, often showing serum elevations in other clinical presentations. More recently, molecular assays targeting prostate disease at the DNA or RNA level have been investigated for potential diagnostic and prognostic utility. With the aid of modern genomics technologies, a variety of molecular biomarkers have been discovered that show potential for specific correlation with prostate cancer. Much of this discovery has been retrospective, using microdissected tissue from prostatectomy. The goal of current research is to apply genomic assays to noninvasive specimens such as blood and urine. Progress in this area is the subject of this review. (C) 2006 Elsevier Ireland Ltd. All rights reserved.

Rice, K. R., et al. (2010). "Evaluation of the ETS-Related Gene mRNA in Urine for the Detection of Prostate Cancer." Clinical Cancer Research 16(5): 1572-1576.

Purpose: Prevalent gene fusions in prostate cancer involve androgen-regulated promoters (primarily TMPRSS2) and ETS transcription factors (predominantly ETS-regulated gene (ERG)], which result in tumor selective overexpression of ERG in two thirds of patients. Because diverse genomic fusion events lead to ERG overexpression in prostate cancer, we reasoned that it may be more practical to capture such alterations using an assay targeting ERG sequences retained in such gene fusions. This study evaluates the potential of an assay quantitating ERG mRNA in post-digital rectal exam (DRE) urine for improving prostate cancer detection. Experimental Design: Patients scheduled to undergo transrectal ultrasound-guided needle biopsy of the prostate were prospectively enrolled. On the day of biopsy, patients provided a urine sample immediately following a DRE. Urine ERG mRNA was measured and normalized to urine prostate-specific antigen (PSA) mRNA using the DTS 400 system. Demographic traits, clinical characteristics and biopsy results were analyzed for association with urine ERG score. Results: The study was conducted on 237 patients. Prostate cancer was shown on biopsy in 40.9% of study subjects. A higher urine ERG score associated significantly with malignancy on biopsy (P = 0.0145), but not with clinical stage or Gleason score. Urine ERG score performed best in Caucasians and in men with a PSA of <= 4 ng/mL (area under the curve = 0.8). Conclusions: A higher urine ERG score in post-DRE urine is associated with the diagnosis of prostate cancer on biopsy. Urine ERG score performed particularly well in men with a PSA of <= 4.0 ng/mL, a segment of the screening population in which further diagnostic markers are needed to determine in whom biopsy should be done. Clin Cancer Res; 16(5); 1572-6. (C)2010 AACR.

Richardsen, E., et al. (2010). "COX-2 is overexpressed in primary prostate cancer with metastatic potential and may predict survival. A comparison study between COX-2, TGF-beta, IL-10 and Ki67." Cancer Epidemiology 34(3): 316-322.

Background: The immune modulating molecules cyclooxygenase-2 (COX-2), transforming growth factor-beta (TGF-beta) and interleukin-10 (IL-10) have regulatory roles in cancer progression. There are conflicting data regarding the roles of these molecules in prostate cancer. To elucidate the prognostic impact of these proteins and provide information on prognosis and treatment, we compared the expression of COX-2, TGF-beta, and IL-10 in prostate cancer specimens with or without metastases. Ki67 was included as a measure of growth fraction of tumor cells. Methods: Digital video analysis images from tumor cell areas and tumor stromal areas were analyzed on formalin fixed, paraffin-embedded and immunohistochemical stained cancer specimens from 59 patients: 32 patients with metastases and 27 patients without clinical, biochemical, or radiological evidence of metastases within 10 years after diagnosis. The expression of COX-2 was scored as negative, weak, moderate, or strong. The expressions of TGF-beta and IL-10 were assessed as proportions of moderately or strongly stained cells. Ki67 was detected as strong nuclear staining in proliferating cells. Results: In primary cancers in the metastatic group, COX2, TGF-beta and Ki67 were stronger expressed in epithelial tumor cell and tumor stromal areas compared with non-metastatic cancers (for all markers, $p < 0.0001$). High intensity of COX-2 staining in tumor areas was strongly associated with death from prostate cancer in univariate analyses (hazard ratio [HR] 95% CI, 4.0 (1.1-14.5)). In multivariate analyses, the risk estimate was strengthened but did not reach significance. No associations to death were found for the other markers. Conclusion: High expression of COX-2, TGF-beta and 1667 were in metastatic primary prostate carcinoma compared to non-metastatic cancers. High expression of COX-2 was associated to death from prostate carcinoma. (c) 2010 Elsevier Ltd. All rights reserved.

Rickman, D. S., et al. (2009). "SLC45A3-ELK4 Is a Novel and Frequent Erythroblast Transformation-Specific Fusion Transcript in Prostate Cancer." Cancer Research 69(7): 2734-2738.
Chromosomal rearrangements account for all erythroblast transformation-specific (ETS) family member gene fusions that have been reported in prostate cancer and have clinical, diagnostic, and prognostic implications. Androgen-regulated genes account for the majority of the 5' genomic regulatory promoter elements fused with ETS genes. TMPRSS2-ERG, TMPRSS2-ETV1, and SLC45A3-ERG rearrangements account for roughly 90% of ETS fusion prostate cancer. ELK4, another ETS family member, is androgen regulated, involved in promoting cell growth, and highly expressed in a subset of prostate cancer, yet the mechanism of ELK4 overexpression is unknown. In this study, we identified a novel ETS family fusion transcript, SLC45A3-ELK4, and found it to be expressed in both benign prostate tissue and prostate cancer. We found high levels of SLC45A3-ELK4 mRNA restricted to a subset of prostate cancer samples. SLC45A3-ELK4 transcript can be detected at high levels in urine samples from men at risk for prostate cancer. Characterization of the fusion mRNA revealed a major variant in which SLC45A3 exon 1 is fused to ELK4 exon 2. Based on quantitative PCR analyses of DNA, unlike other ETS fusions described in prostate cancer, the expression of SLC45A3-ELK4 mRNA is not exclusive to cases harboring a chromosomal rearrangement. Treatment of LNCaP cancer cells with a synthetic androgen (111881) revealed that SLC45A3-ELK4, and not endogenous ELK4, mRNA expression is androgen regulated. Altogether, our findings show that SLC45A3-ELK4 mRNA expression is heterogeneous, highly induced in a subset of prostate cancers, androgen regulated, and most commonly occurs through a mechanism other than chromosomal rearrangement (e.g., trans-splicing). [Cancer Res 2009;69(7):2734-8]

Rigau, M., et al. (2010). "PSGR and PCA3 as Biomarkers for the Detection of Prostate Cancer in Urine." Prostate 70(16): 1760-1767.

BACKGROUND. Several studies have demonstrated the usefulness of monitoring an RNA transcript in urine, such as PCA3, for prostate cancer (PCa) diagnosis. PCa screening would benefit from additional biomarkers of higher specificity and could be used in conjunction with prostate-specific antigen (PSA) testing, in order to better determine biopsy candidates. METHODS. We used urine sediments after prostate massage (PM) from 215 consecutive patients, who presented for prostate biopsy. We tested whether prostate-specific G-protein coupled receptor (PSGR), a biomarker previously described to be over-expressed in PCa tissue, could also be detected by quantitative real-time PCR in post-PM urine sediment. We combined these findings with prostate cancer gene 3 (PCA3), the current gold standard for PCa diagnosis in urine, to test if a combination of both biomarkers could improve the sensitivity of PCA3 alone. RESULTS. By univariate analysis we found that PSGR and PCA3 were significant predictors of PCa. Receiver operator characteristic curve analysis and its multivariate extension, multivariate ROC (MultiROC), were used to assess the outcome predictive values of the individual and the paired biomarkers. We obtained the following area under the curve values: PSA (0.602), PSGR (0.681), PCA3 (0.656), and PSGRvPCA3 (0.729). Then, we tested whether a combination of PSGR and PCA3 could improve specificity by fixing the sensitivity at 95%. We obtained specificities of 15% (PSGR), 17% (PCA3), and 34% (PSGRvPCA3). CONCLUSIONS. A multiplexed model including PSGR and PCA3 improves the specificity for the detection of PCa, especially in the area of high sensitivity. This could be clinically useful for determining which patients should undergo biopsy. Prostate 70:1760-1767, 2010. (C) 2010 Wiley-Liss, Inc.

Risk, M. C. and D. W. Lin (2009). "New and novel markers for prostate cancer detection." Current urology reports 10(3): 179-186.
The detection and treatment of prostate cancer was dramatically altered with the advent of the prostate-specific antigen (PSA), and its usefulness particularly in following patients after radical prostatectomy is unquestioned. The ability of PSA to predict prostate cancer, and in particular clinically relevant prostate cancer, has come into doubt in recent years and has led to the search for better diagnostic markers for prostate cancer. Both serum and urine biomarkers are in various stages of development, and many of these have been discovered through progress in genomic and proteomic analysis. Some of these perform better in limited study than our current standards of diagnosis (ie, PSA and digital rectal examinations), and some have suggested the capacity to predict stage and likelihood of recurrence. Further study is needed to validate many of these markers, and the future of prostate cancer detection will likely lie in multiplex assays that test a number of markers concomitantly to assess prostate cancer risk.

Roato, I., et al. (2008). "Osteoclasts Are Active in Bone Forming Metastases of Prostate Cancer Patients." PloS one 3(11).
Background: Bone forming metastases are a common and disabling consequence of prostate cancer (CaP). The potential role of osteoclast activity in CaP bone metastases is not completely explained. In this study, we investigated ex vivo whether the osteolytic activity is present and how it is ruled in CaP patients with bone forming metastases. Methodology: Forty-six patients affected by newly diagnosed CaP and healthy controls were enrolled. At diagnosis, 37 patients had a primary tumour only, while 9 had primary tumour and concomitant bone forming metastases. In all patients there was no evidence of metastasis to other non-bone sites. For all patients and controls we collected blood and urinary samples. We evaluated patients' bone homeostasis; we made peripheral blood mononuclear cell (PBMC) cultures to detect in vitro osteoclastogenesis; we dosed serum expression of molecules involved in cancer induced osteoclatogenesis, such as RANKL, OPG, TNF-alpha, DKK-1 and IL-7. By Real-Time PCR, we quantified DKK-1 and IL-7 gene expression on micro-dissected tumour and healthy tissue sections. Principal Findings: CaP bone metastatic patients showed bone metabolism disruption with increased bone resorption and formation compared to non-bone metastatic patients and healthy controls. The CaP PBMC cultures showed an enhanced osteoclastogenesis in bone metastatic patients, due to an increase of RANKL/OPG ratio. We detected increased DKK-1 serum levels and tissue gene expression in patients compared to controls. IL- 7 resulted high in patients' sera, but its tissue gene expression was comparable in patients and controls. Conclusions: We demonstrated ex vivo that osteoclastogenesis is an active mechanism in tumour nesting of bone forming metastatic cancer and that serum DKK-1 levels are increased in CaP patients, suggesting to deeply investigate its role as tumour marker.

Robert, G., et al. (2013). "Rational basis for the combination of PCA3 and TMPRSS2:ERG gene fusion for prostate cancer diagnosis." Prostate 73(2): 113-120.

BACKGROUND The prostate cancer gene 3 (PCA3) and TMPRSS2:ERG gene fusion are promising prostate cancer (PCa) specific biomarkers. Our aim was to simultaneously quantify the expression levels of PCA3 and TMPRSS2:ERG in a panel of benign prostatic hyperplasia (BPH), normal prostate adjacent to PCa (NP) and PCa tissue samples, to provide a rational basis for the understanding of the false-positive and false-negative results of the urine assays. METHODS The tissue samples were carefully histopathologically characterized to obtain homogeneous groups. The mRNA was isolated, transcribed into cDNA and the relative expressions of PCA3 and TMPRSS2:ERG were measured using a quantitative real-time polymerase chain reaction. The expression levels of PCA3 and TMPRSS2:ERG were compared between the different groups. RESULTS We included 48 BPH, 32 NP, and 48 PCa. The PCA3 expression levels progressively increased from BPH to NP (3 times) and finally to PCa (30 times). There were one false-positive sample and seven false-negative samples. The TMPRSS2:ERG gene fusion was found in 8.3% of the BPH, 15.6% of the NP, and 50% of the PCa samples. The use of TMPRSS2:ERG in the PCA3 negative cases allowed diagnosis of four of the seven false-negative samples and added one false-positive, but we had to define a cut-off value to avoid eight false-positive results. CONCLUSIONS Considering tissue expression of the markers, most of the false-negative results of the PCA3 test were corrected by TMPRSS2:ERG (57%) and the combination of both had a higher sensitivity for PCa diagnosis. Some of the control samples did express TMPRSS2:ERG and a cut-off value had to be defined to avoid false-positive results. Prostate 73: 113120, 2013. (c) 2012 Wiley Periodicals, Inc.

Ronnau, C. G. H., et al. (2014). "Noncoding RNAs as novel biomarkers in prostate cancer." BioMed research international 2014: 591703-591703.

Prostate cancer (PCa) is the second most common diagnosed malignant disease in men worldwide. Although serum PSA test dramatically improved the early diagnosis of PCa, it also led to an overdiagnosis and as a consequence to an overtreatment of patients with an indolent disease. New biomarkers for diagnosis, prediction, and monitoring of the disease are needed. These biomarkers would enable the selection of patients with aggressive or progressive disease and, hence, would contribute to the implementation of individualized therapy of the cancer patient. Since the FDA approval of the long noncoding PCA3 RNA-based urine test for the diagnosis of PCa patients, many new noncoding RNAs (ncRNAs) associated with PCa have been discovered. According to their size and function, ncRNAs can be divided into small and long ncRNAs. NcRNAs are expressed in (tumor) tissue, but many are also found in circulating tumor cells and in all body fluids as protein-bound or incorporated in extracellular vesicles. In these protected forms they are stable and so they can be easily analyzed, even in archival specimens. In this review, the authors will focus on ncRNAs as novel biomarker candidates for PCa diagnosis, prediction, prognosis, and monitoring of therapeutic response and discuss their potential for an implementation into clinical practice.

Roobol, M. J., et al. (2011). "Tumour markers in prostate cancer III: Biomarkers in urine." Acta Oncologica 50: 85-89.

The serum PSA test still is the most important biomarker for the detection and follow-up of prostate cancer. PSA-based screening can reduce disease specific mortality but coinciding unnecessary testing and overdiagnosis warrant further research for more specific biomarkers. Numerous studies of both serum and urine-based prostate cancer biomarker candidates have been presented the last ten years. However, biomarkers for identifying the most aggressive subsets of this malignancy are still missing. Being non-invasive, urine-based tests might be suitable for both clinical and (mass) screening purposes, but also for prediction and to gain prognostic information. Protein-based, DNA-based and RNA-based urine biomarkers have been developed and tested. Protein markers in urine. Data on protein-based urine biomarkers (i.e. Annexin A3, matrix metalloproteinases and the urinary: serum PSA ratio) show up to now contradictory results and further studies are warranted to be able to assess their clinical value in which the cost aspect should not be overlooked. DNA markers in urine. Studies on DNA-based urine biomarkers focus on hypermethylation of gene panels with GSTP1 hypermethylation being the most promising individual marker. Larger prospective clinical studies of single markers and gene panels are however needed to validate their clinical utility. RNA markers in urine. 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 combination have been subject of many studies showing encouraging results. Conclusion. Up to now urine-based biomarkers represent a promising alternative or addition to serum-based biomarkers. Prospective studies in a multivariate setting, including larger sample sizes and avoiding attribution bias caused by preselection on the basis of serum PSA are however required.

Rostad, K., et al. (2009). "TMPRSS2:ERG fusion transcripts in urine from prostate cancer patients correlate with a less favorable prognosis." Apmis 117(8): 575-582.

The transcription factor ERG is highly upregulated in the majority of prostate cancers due to chromosomal fusion of the androgen responsive promoter of TMPRSS2 to the ERG reading frame. Our aim was to identify this gene fusion in urine samples from prostate cancer patients prior to radical treatment and to compare fusion status with clinicopathological variables. Urine fractions from 55 patients (with and without prior prostatic massage) were analyzed for the presence of TMPRSS2:ERG isoforms using real-time qPCR. Sixty-nine percent of urine samples following prostatic massage were positive for TMPRSS2:ERG isoforms a or b, five out of which were positive for both, vs 24% of samples obtained without prior massage. Isoform a seems to be most prevalent and some patients may be positive for more than one fusion variant, reflecting the multifocality of prostate cancer. Prostatic massage prior to sampling, analysis of pelleted urine material and detection of cDNA provided the highest sensitivity. Positive statistical correlations were identified between TMPRSS2:ERG fusion and high s-PSA, pathological stage and Gleason score. Our findings contribute to the increasing elucidation of the role of TMPRSS2:ERG in the development of prostate cancer.

Russo, A. L., et al. (2009). "Urine Analysis and Protein Networking Identify Met as a Marker of Metastatic Prostate Cancer." Clinical Cancer Research 15(13): 4292-4298.

Purpose: Metastatic prostate cancer is a major cause of death of men in the United States. Expression of met, a receptor tyrosine kinase, has been associated with progression of prostate cancer. Experimental Design: To investigate met as a biomarker of disease progression, urinary met was evaluated via ELISA in men with localized (n = 75) and metastatic (n = 81) prostate cancer. Boxplot analysis was used to compare the distribution of met values between each group. We estimated a receiver operating characteristic curve and the associated area under the curve to summarize the diagnostic accuracy of met for distinguishing between localized and metastatic disease. Protein-protein interaction networking via yeast two-hybrid technology supplemented by Ingenuity Pathway Analysis and Human Interactome was used to elucidate proteins and pathways related to met that may contribute to progression of disease. Results: Met distribution was significantly different between the metastatic group and the group with localized prostate cancer and people with no evidence of cancer (P < 0.0001). The area under the curve for localized and metastatic disease was 0.90, with a 95% confidence interval of 0.84 to 0.95. Yeast two-hybrid technology, Ingenuity Pathway Analysis, and Human Interactome identified 89 proteins that interact with met, of which 40 have previously been associated with metastatic prostate cancer. Conclusion: Urinary met may provide a noninvasive biomarker indicative of metastatic prostate cancer and may be a central regulator of multiple pathways involved in prostate cancer progression.

Russo, G., et al. (2008). "p53 Gene Mutational Rate, Gleason Score, and BK Virus Infection in Prostate Adenocarcinoma: Is There a Correlation?" Journal of Medical Virology 80(12): 2100-2107.

Prostate cancer represents the second leading cause of cancer deaths in Western countries. Viral infections could play a role in prostate carcinogenesis. Human polyomavirus BK (BKV) is a possible candidate because of its transforming properties. In this study, BKV sequences in urine, blood, fresh, and paraffin-em bedded prostate cancer samples from 26 patients were searched using Q-PCR analysis. T antigen (TAg) and p53 localization in neoplastic cells were evaluated by immunohistochemical analysis. Also, the presence of mutations in 5-9 exons of p53 gene was analyzed. Results showed that BKV-DNA was found in urine (54%), plasma (31%), and in fresh prostate cancer specimens (85%). The analysis of p53 gene evidenced several mutations in high Gleason patients, according to tumor advanced stage. Immunohistochemical analysis results evidenced the localization of p53 and TAg into cytoplasm, whereas in TAg-negative tumors, p53 was nuclear. This study suggests that BKV acts as cofactor in the pathogenesis of prostate cancer. These observations emphasize previous studies regarding the cellular pathways that may be deregulated by BKV. J. Med. Virol. 80:2100-2107,2008. (C) 2008 Wiley-Liss, Inc.

Sabaliauskaite, R., et al. (2012). "Combined analysis of TMPRSS2-ERG and TERT for improved prognosis of biochemical recurrence in prostate cancer." Genes Chromosomes & Cancer 51(8): 781-791.

Prostate cancer (PCa) is a heterogeneous disease with diverse clinical outcomes. TMPRSS2ERG is the most common gene fusion in PCa, whereas activation of telomerase is a common feature of various malignancies. The aim of our study was to explore the combined utility of these and some other biomarkers in predicting biochemical recurrence after radical prostatectomy. Prostate specimens and urine sediments from 179 previously untreated patients with pT2-pT3 stage PCa were analyzed for expression of telomerase (TERT and TR) and the TMPRSS2ERG fusion gene by means of reverse transcription PCR. Real-time PCR was used for quantification of ERG and SPINK1 expression. In total, 74% (117/158) of the prostate adenocarcinomas were positive for the TMPRSS2ERG and/or TERT expression. Noninvasively, these transcripts were identified in 31% (19/61) of catheterized urine specimens. Significantly higher expression of ERG was detected in TMPRSS2ERG-positive tumors (P < 0.0001), whereas more intense expression of SPINK1 was characteristic for the TMPRSS2ERG-negative tumors (P = 0.003). TERT-positive cases also had elevated levels of ERG (P = 0.016), suggesting a possible link between aberrant expression of ERG and reactivation of TERT in prostate tumors. The cases negative for both transcripts, TMPRSS2ERG and TERT, rarely recurred (P = 0.014) and showed significantly longer biochemical recurrence-free period (P = 0.022) as compared to the TMPRSS2ERG and/or TERT-positive cases. The results of our study suggest that combined analysis of TMPRSS2ERG and TERT expression can be a valuable tool for early prediction of biochemical recurrence of PCa after radical prostatectomy. (c) 2012 Wiley Periodicals, Inc.

Saeki, N., et al. (2010). "Prostate Stem Cell Antigen: A Jekyll and Hyde Molecule?" Clinical Cancer Research 16(14): 3533-3538.

Prostate stem cell antigen (PSCA) is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein. Although PSCA is thought to be involved in intracellular signaling, much remains unknown about its physiological function and regulatory mechanism in normal and cancer cells. It is up-regulated in several major cancers including prostate, bladder, and pancreatic cancers. The expression of PSCA is positively correlated with advanced clinical stage and metastasis in prostate cancers and is also associated with malignant progression of premalignant prostate lesions. Therefore, PSCA has been proposed as a biomarker of diagnosis and prognosis, as well as a target of therapy for these cancers. In addition, PSCA has also shown clinical potential in immunotherapy as a prostate-specific antigen, which, when presented by dendritic cells, may elicit strong tumor-specific immunity. In contrast, PSCA is down-regulated in esophageal and gastric cancer and may have a tumor-suppressing function in the gastric epithelium. Recent exciting findings that genetic variations of PSCA conferred increased risks of gastric cancer and bladder cancer have opened up a new avenue of research about the pathological function of PSCA. PSCA seems to be a Jekyll and Hyde molecule that plays differential roles, tumor promoting or suppressing, depending on the cellular context. Clin Cancer Res; 16(14); 3533-8. (C) 2010 AACR.

Salagierski, M. and J. A. Schalken (2012). "Molecular Diagnosis of Prostate Cancer: PCA3 and TMPRSS2:ERG Gene Fusion." Journal of Urology 187(3): 795-801.

Purpose: Widespread prostate specific antigen screening together with the increase in the number of biopsy cores has led to increased prostate cancer incidence. Standard diagnostic tools still cannot unequivocally predict prostate cancer progression, which often results in a significant overtreatment rate. We present recent findings on PCA3 and TMPRSS:ERG fusion, and describe their clinical implications and performance. Materials and Methods: The PubMed(R) database was searched for reports on PCA3 (130 articles), TMPRSS:ERG and ETS fusion (180 publications) since 1999. Results: In recent years advances in genetics and biotechnology have stimulated the development of noninvasive tests to detect prostate cancer. Serum and urine molecular biomarkers have been identified, of which PCA3 has already been introduced clinically. The identification of prostate cancer specific genomic aberrations, ie TMPRSS2:ERG gene fusion, might improve diagnosis and affect prostate cancer treatment. Conclusions: Although several recently developed markers are promising, often showing increased specificity for prostate cancer detection compared to that of prostate specific antigen, their clinical application is limited. The only 2 true prostate cancer specific biomarkers identified to date remain PCA3 and TMPRSS2:ERG gene fusion.

Salami, S. S., et al. (2013). "Combining urinary detection of TMPRSS2:ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer." Urologic Oncology-Seminars and Original Investigations 31(5): 566-571.

Objectives: We sought to develop a clinical algorithm combining serum PSA with detection of TMPRSS2:ERG fusion and PCA3 in urine collected after digital rectal exam (post-DRE urine) to predict prostate cancer on subsequent biopsy. Materials and methods: Post-DRE urine was collected in 48 consecutive patients before prostate biopsy at 2 centers; quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used to detect PCA3 and TMPRSS2:ERG fusion transcript expression. Serum PSA was measured by clinical assay. The performance of TMPRSS2:ERG fusion, PCA3, and serum PSA as biomarkers predicting prostate cancer at biopsy was measured; a clinically practical algorithm combining serum PSA with TMPRSS2:ERG and PCA3 in post-DRE urine to predict prostate cancer was developed. Results: Post-DRE urine sediment provided informative RNA in 45 patients; prostate cancer was present on subsequent biopsy in 15. TMPRSS2:ERG in post-DRE urine was associated with prostate cancer (OR = 12.02; P < 0.001). PCA3 had the highest sensitivity in predicting prostate cancer diagnosis (93%), whereas TMPRSS2:ERG had the highest specificity (87%). TMPRSS2:ERG had the greatest discriminatory value in predicting prostate cancer (AUC = 0.77 compared with 0.65 for PCA3 and 0.72 for serum PSA alone). Combining serum PSA, PCA3, and TMPRSS2:ERG in a multivariable algorithm optimized for clinical utility improved cancer prediction (AUC = 0.88; specificity = 90% at 80% sensitivity). Conclusions: A clinical algorithm specifying biopsy for all patients with PSA >= 10 ng/ml, while restricting biopsy among those with PSA <10 ng/ml to only those with detectable PCA3 or TMPRSS2:ERG in post-DRE urine, performed better than the individual biomarkers alone in predicting prostate cancer. (C) 2013 Elsevier Inc. All rights reserved.

Sardana, G. and E. P. Diamandis (2009). "The kallikrein family of proteins as urinary biomarkers for the detection of prostate cancer." Clinical Biochemistry 42(13-14): 1483-1486.
Background: Several urinary biomarkers have been assessed as showing a discriminatory ability to differentially diagnose prostate cancer, albeit with manipulation of the prostate. Here we examine the clinical utility of multiple members of the kallikrein family of proteins in non-manipulative urinary biomarker testing. Methods: Forty urine samples were collected from patients admitted for urological examination. Twenty, with a confirmed benign diagnosis and 20 with prostate cancer. The levels of 14 kallikrein proteins were measured in patient's urine and normalized for creatinine. Results: Ten of the 14 kallikreins tested had detectable levels in urine. However, none showed statistical significance in discriminating patients. Serum PSA was superior to urine PSA and other urinary kallikreins in separating patients with and without prostate cancer. Conclusions: We were unable to distinguish men with and without prostate cancer using multiple kallikreins as urinary biomarkers. These results highlight the difficulties in diagnosing prostate cancer via urine testing for soluble biomarkers. (C) 2009 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Sardana, G. and E. P. Diamandis (2012). "Biomarkers for the diagnosis of new and recurrent prostate cancer." Biomarkers in Medicine 6(5): 587-596.
Prostate cancer is the most prevalent cancer in men and can be managed effectively if diagnosed early and monitored. Currently, prostate-specific antigen testing in conjunction with a digital rectal exam has been utilized for screening at-risk men. However, the lack of specificity of prostate-specific antigen as a marker for prostate cancer combined with the asymptomatic and slow-growing nature of prostate tumors has resulted in many men being overdiagnosed and subjected to surgery or treatment with adverse side effects. The focus in the research community currently has been on discovering noninvasive surrogate markers such as proteins, circulating tumor cells and nucleic acids in the blood or urine of patients with prostate cancer. These markers, in combination with prostate-specific antigen, are providing promise that a personalized multiparametric approach to prostate cancer diagnosis and monitoring will aid in managing this disease.

Sardareh, H. M., et al. (2014). "Prostate Cancer Antigen 3 Gene Expression in Peripheral Blood and Urine Sediments from Prostate Cancer and Benign Prostatic Hyperplasia Patients versus Healthy Individuals." Urology Journal 11(6): 1952-1958.

Purpose: To determine the expression of prostate cancer antigen 3 (PCA3) gene in peripheral blood and urine sediments from patients with prostate cancer (PCa) and benign prostatic hyperplasia (BPH) and normal subjects. Materials and Methods: A total number of 48 patients [24 with biopsy proven prostate cancer (PCa) and 24 with benign prostate hyperplasia (BPH)] were studied. Twenty-four healthy individuals were also recruited as control group. After blood and urine sampling, total RNA was extracted and cDNA was synthesized. Expression of PCA3 gene was assessed by quantitative reverse transcription polymerase chain reaction. Results: Comparison of PCA3 gene expression between control and BPH groups indicated no statistically significant differences in both urine and blood samples. Patients with PCa demonstrated an increased PCA3 gene expression rate compared to control and BPH groups (10.64 and 7.17 folds, respectively). The rate of fold increased PCA3 gene expression in urine was 20.90, 20.90, and 20.35 in patients with PCa, BPH and normal subjects, respectively. Conclusion: Evaluation of PCA3 gene expression can be considered as a reliable marker for detection of PCa. Increased level of this marker in urine sediments is more sensitive than blood for distinguishing between cancerous and non-cancerous groups.

Sato, I., et al. (2007). "Seasonal changes in urinary prostate-specific antigenic activity in male Japanese Macaques (Macaca fuscaa fuscata)." Journal of Andrology 28(6): 821-826.
Prostate-specific antigen (PSA) is usually detected in male adult urine and semen according to the Tanner stage development of males from birth to adolescence. To further study the pituitary-testicular axis in males, we determined urinary PSA levels in pr;imates. Urinary PSA was detected with the use of antihuman PSA monoclonal antibody in male adult Japanese macaques (Macaca fuscaa fuscata) of seasonal breeding status. PSA activity in aseasonal animals (crab-eating macaques, Macaca fascisularis) did not change throughout the year; however, alterations in PSA activity were observed in Japanese macaques during breeding season, with the highest levels observed between October and January, the lowest levels between January and June, and a gradual increase in PSA activity observed from August until October. Although primate urinary PSA produces 2 polypeptide bands of approximately 55 and 33 kd, in addition to a band corresponding to human urinary PSA, the 33-kd polypeptide band was less pronounced during nonbreeding season in Japanese macaques. Urinary testosterone (T) levels in seasonally breeding animals (Japanese macaques) changed in parallel with urinary PSA levels. When urinary PSA and T levels were compared among animals during the breeding season (from October to February) and the nonbreeding season (from March to September), significantly increased PSA and T levels were observed during the breeding season. Furthermore, PSA and T levels in a monkey housed in a cage placed between 2 female cages were elevated compared with other monkeys. Increased PSA activity was observed concurrent with menstrual blood loss in females. These results suggest a link between PSA activity and testosterone levels, which could be influenced by changes in the female menstrual cycle.

Schalken, J. A. (2009). "Towards Early and More Specific Diagnosis of Prostate Cancer? Beyond PSA: New Biomarkers Ready for Prime Time." European Urology Supplements 8(3): 97-102.

Context: The current standard for early detection of prostate cancer (PCa) consists of a digital rectal examination (DRE) and a serum test for prostate-specific antigen (PSA). However, there is no definitive PSA level that can accurately differentiate men with cancer from men with benign prostatic hyperplasia. A large population of men with chronically elevated serum PSA and one or more negative prostate biopsies has now emerged who are at risk of developing clinically significant prostate cancer as they age. However, serum PSA and its derivative assays may not allow effective monitoring of these patients for PCa, and many consequently undergo repeat biopsies. While prostate biopsy remains the gold standard for PCa diagnosis, this method has its own limitations and associated comorbidities. Objective: More accurate diagnostic tests are needed to help guide decisions to biopsy the prostate, and recent developments are reviewed in this paper. Evidence acquisition: Publications on prostate cancer gene 3 (PCA3) since 1999, the date the gene was described for the first time. Evidence synthesis: Direct detection of cancer cells in biological fluids is attractive due to the expected improvement in specificity compared with the measurement of surrogate protein markers in blood. in addition, gene-based assays for cancer cell detection should be synergistic with immunoassays for blood antigens. PCA3 levels in urine is the first commercially available noninvasive molecular test for the diagnosis of PCa and therefore provides a case study for the successful translation of a molecular marker from the research laboratory to clinical practice. Conclusions: This paper describes the development of PCA3-based molecular urine tests, and we also review the most recent data demonstrating the potential diagnostic and prognostic utilities of PCA3 and the initial findings of the TMPRSS2-ERG gene fusion testing. (C) 2008 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Schenk, J. M., et al. (2010). "Biomarkers of Systemic Inflammation and Risk of Incident, Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial." American Journal of Epidemiology 171(5): 571-582.

The authors conducted a nested case-control study of serum inflammatory markers and risk of symptomatic benign prostatic hyperplasia (BPH), using data from the placebo arm of the Prostate Cancer Prevention Trial (1993-2003). Incident BPH (n = 676) was defined as treatment, report of 2 International Prostate Symptom Score (IPSS) values > 14, or 2 increases of >= 5 from baseline values with at least one value >= 12. Controls (n = 683) were men who reported no BPH treatment or IPSS values > 7 over the 7-year trial. Baseline serum was analyzed for C-reactive protein, tumor necrosis factor alpha (monomer), soluble tumor necrosis factor receptors I and II (sTNF-RI and sTNF-RII), interleukin 6, and interferon gamma. Controlled for age and race, a high C-reactive protein concentration was associated with increased BPH risk (for quartile 4 vs. quartile 1, odds ratio (OR) = 1.40, 95% confidence interval (CI): 1.04, 1.88); this was attenuated after control for body mass index (OR = 1.30, 95% CI: 0.95, 1.75). Low sTNF-RII and high interleukin 6 concentrations were associated with increased BPH risk (for quartile 4 vs. quartile 1, sTNF-RII: OR = 0.61, 95% CI: 0.46, 0.82; interleukin 6: OR = 1.79, 95% CI: 1.32, 2.42); these associations were only in men aged < 65 years. Results suggest that systemic inflammation or lower levels of soluble receptors that bind inflammatory cytokines increase BPH risk.

Schenk, J. M., et al. (2009). "Serum Adiponectin, C-Peptide and Leptin and Risk of Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial." Prostate 69(12): 1303-1311.

BACKGROUND. Recent epidemiologic studies have identified obesity as a risk factor for benign prostatic hyperplasia (BPH). We examined whether adiponectin, leptin, and C-peptide were associated with incident, symptomatic BPH and whether these factors mediate the relationship between obesity and BPH risk. METHODS. Data are from Prostate Cancer Prevention Trial placebo arm participants who were free of BPH at baseline. incident BPH (n = 698) was defined as treatment, two International Prostate Symptom Score (IPSS) values > 14, or an increase of >= 5 in IPSS from baseline documented on at least two occasions Plus at least one score >= 12. Controls (n = 709) were selected from men reporting no BPH treatment or IPSS > 7 during the 7-year trial. Baseline serum was analyzed for adiponectin, C-peptide, and leptin concentrations. RESULTS. Neither C-peptide nor leptin was associated with BPH risk. The odds ratio 195% CI] contrasting highest to lowest quartiles of adiponectin was 0.65[0.47, 0.87] P(trend)=0.004. Findings differed between levels of physical activity: there was a strong inverse association between adiponectin and BPH among moderately/very active men OR = 0.43 [0.29, 0.63], and no association among sedentary/minimally active men OR = 0.92 [0.65,130] P(interaction) = 0.005. Adiponectin concentrations explained only a moderate amount of the relationship between obesity and BPH risk. CONCLUSIONS. High adiponectin concentrations were associated with reduced risk of incident, symptomatic BPH. This association was limited to moderately/very active men; suggesting the relationship between obesity and BPH involves a complex interaction between factors affecting glucose uptake and insulin sensitivity. However, adiponectin is likely not the only mechanism through which obesity affects BPH risk. Prostate 69:1303-1311, 2009. (C) 2009 Wiley-Liss, Inc.

Schiffer, E. (2007). "Biomarkers for prostate cancer." World Journal of Urology 25(6): 557-562.

Novel biomarkers for prostate cancer (PCa) are currently being assessed for utility in PCa diagnosis. This article aims to provide concise information on the current findings that impact prostate cancer research. Results of enzyme-linked immunosorbent assays (ELISA) for single biomarkers, quantitative polymerase chain reaction (PCR)-based assays for DNA/RNA markers will be reviewed in addition to high-throughput proteomic profiling of PCa specimens. The advantages/disadvantages of tissue, blood, urine or seminal plasma as sources for potential biomarkers are discussed emphasizing the consequences for PCa diagnosis. In summary, the majority of promising marker candidates available today needs further validation. Some of the identified markers have the potential to yield novel prognostic tools for PCa, provide novel insights into its pathophysiology, and contribute to the establishment of novel treatment strategies.

Schiffer, E., et al. (2012). "Urinary proteome analysis for prostate cancer diagnosis: Cost-effective application in routine clinical practice in Germany." International Journal of Urology 19(2): 118-125.

Objectives: Capillary electrophoresis mass spectrometry urinary proteome analysis for prostate cancer has been shown to be highly accurate in the detection of prostate cancer. The aim of the present study was to report our experience with routine application of this test in clinical practice and its cost-effectiveness. Methods: The urinary proteome analysis for prostate cancer test was carried out in 211 patients in outpatient centers. In 184 of them, data about their followup and the test results were available for analysis. Prostate cancer was detected in 49 cases. Results: The test correctly recognized 42 out of 49 tumor patients, showing a sensitivity of 86% (95% confidence interval 73-94). Of 135 prostate cancer-negative patients, 79 had a negative urinary proteome analysis for prostate cancer test (specificity 59% [79/135 95% confidence interval 50-66]). Negative and positive predictive values were 92% (95% confidence interval 84-96) and 43% (95% confidence interval 33-53), respectively. A statistically significant (P < 0.0005) improvement in terms of diagnostic accuracy was observed in comparison with serum prostate-specific antigen and percent-free prostate-specific antigen. Whereas the urinary proteome analysis for prostate cancer test results agreed in 65.7% with follow-up reference results, prostate-specific antigen achieved 33.3% and percent-free prostate-specific antigen achieved 42.7%. Cost-effectiveness analysis showed that the urinary proteome analysis for prostate cancer strategy outperformed the biopsy approach as well as prostate-specific antigen tests. Conclusions: The non-invasive urinary proteome analysis for prostate cancer test appears to be a helpful addition to prostate cancer diagnostics for patients with suspicious prostate-specific antigen and/or digital-rectal examination.

Schmidt, F., et al. (2009). "Gene fusion in prostate cancer - clinical applications in diagnosis, prognosis and therapy." Deutsche Medizinische Wochenschrift 134(28-29): 1483-1486.

Scholtysek, C., et al. (2009). "Characterizing components of the Saw Palmetto Berry Extract (SPBE) on prostate cancer cell growth and traction." Biochemical and Biophysical Research Communications 379(3): 795-798.

Saw Palmetto Berry Extract (SPBE) is applied for prostate health and treatment of urinary tract infections. nonbacterial prostitis and Benign Prostatic Hyperplasia (BPH) in man. An assumption is that SPBE affects tumor cell progression and migration in breast and prostate tissue. In this work, DU-145 cells were used to demonstrate that SPBE and its sterol components, p-sitosterol and stigmasterol, inhibit prostate cancer growth by increasing p53 protein expression and also inhibit carcinoma development by decreasing p21 and p27 protein expression. In the presence of cholesterol. these features are not only reversed but increased significantly. The results Show for the first time the potential of SPBE, beta-sitosterol and stigmasterol as potential anti-tumor agents. Since the protein p53 is also regarded as nuclear matrix protein facilitating actin cytoskeletal binding, 2D tractions were measured. The cell adhesion strength in the presence of SPBE, beta-sitosterol and cholesterol and the observation was that the increase in p53 expression triggered an increase in the intracellular force generation. The results Suggest a dual function of p53 in cells. (c) 2008 Elsevier Inc. All rights reserved.

Sfanos, K. S., et al. (2009). "Acute inflammatory proteins constitute the organic matrix of prostatic corpora amylacea and calculi in men with prostate cancer." Proceedings of the National Academy of Sciences of the United States of America 106(9): 3443-3448.

Corpora amylacea (CA) are a frequent microscopic finding in radical prostatectomy specimens from men undergoing treatment for prostate cancer. Although often observed histologically to be associated with inflammation, the contribution of CA to prostatitis-related symptoms of unknown etiology or to prostate carcinogenesis remains unclear. Prostatic calculi (PC), which potentially represent calcified forms of CA, are less common but can cause urological disease including urinary retention and prostatitis. We conducted a comprehensive compositional analysis of CA/PC to gain insight into their biogenesis. Infrared spectroscopy analysis of calculi collected from 23 patients confirmed a prevalence of calcium phosphate in the form of hydroxyapatite. This result sets PC apart from most urinary stones, which largely are composed of calcium oxalate. Tandem mass spectrometry-based proteomic analysis of CA/PC revealed that lactoferrin is the predominant protein component, a result that was confirmed by Western blot analysis. Other proteins identified, including calprotectin, myeloperoxidase, and alpha-defensins, are proteins contained in neutrophil granules. Immunohistochemistry (IHC) suggested the source of lactoferrin to be prostate-infiltrating neutrophils as well as inflamed prostate epithelium; however, IHC for calprotectin suggested prostate-infiltrating neutrophils as a major source of the protein, because it was absent from other prostate compartments. This study represents a definitive analysis of the protein composition of prostatic CA and calculi and suggests that acute inflammation has a role in their biogenesis-an intriguing finding, given the prevalence of CA in prostatectomy specimens and the hypothesized role for inflammation in prostate carcinogenesis.

Shafiee, R., et al. (2015). "Diagnostic investigations of canine prostatitis incidence together with benign prostate hyperplasia, prostate malignancies, and biochemical recurrence in high-risk prostate cancer as a model for human study." Tumor Biology 36(4): 2437-2445.

The aim of this study was to evaluate the prevalence of acute and chronic inflammation, benign prostatic hyperplasia (BPH), and cancer of the prostate glands in the canine as a human model in prostate disorders. The study was carried out on 12 cases of different male dogs of terrier (50 %), German shepherd (25 %) breeds, and Greden (25 %), and the age of the dogs ranged from 6 to 13 years (average age 7.8 +/- 3.6). The bodyweight ranged from 3.6 to 7.9 kg. Signalment, clinical signs, and diagnostic tools such as ultrasonography, urinary cytology, and histopathology are presented. Dysuria was the most common clinical sign in this study and occurred in 10/12 canine (83.3 %) included. Other clinical signs included lameness (5/12 canine, 41.6 %) and constipation (3/12 canine, 25 %). The range of duration of clinical signs was 5 days to 7 months. Moreover, in the present study, the urinary biochemical markers of different prostate lesions include blood, protein, and glucose and were detected in 11/12 cases (91.6 %), 5/12 cases (41.6 %), and 2/12 cases (16.6 %), respectively. Taken together, sonographic data were classified into four groups based on histological diagnosis. In 7/12 cases (58.4 %), the prostate appeared to have BPH lesions, and the remaining lesions included inflammation (3/12 cases, 25 %), abscess (1 case, 8.3 %), and adenocarcinoma (1 case, 8/3 %) on ultrasound. In all cases, prostate tissue had an irregular echotexture. None of the dogs had sonographic evidence of sublumbar lymph node enlargement. Histopathologically, we looked at the prevalence of inflammation (33.3 % chronic and 8.3% acute) and BPH (58.4 %) in dogs of different ages and breeds, and also, we observed chronic inflammation in >20 % of dogs, which was about 25 % in 3 cases of the 12 cases referred. More chronic inflammation was associated with more BPH. The majority of the asymptomatic inflammation that is detected in the prostate is classified as chronic inflammation (i.e., as evidenced by the presence of monocytic and/or lymphoplasmacytic inflammatory cell infiltrates); however, acute inflammation is also observed to a lesser degree. Acute inflammation, as is typically evidenced by the infiltration of neutrophils, is classically an indicator of an infectious process. Finally, the patients included seven castrated, four castrated together with antibiotic therapy, and one castrated together with chemotherapy intact male dogs, which were treated with the mentioned cases. In conclusion, chronic prostatic inflammation could be a central mechanism in BPH progression, but the pathological features of tissue inflammation were different between BPH and prostate cancer (PCa). Nevertheless, the histological examination of prostate biopsies remains the only way to diagnose prostatic disorders.

Shariat, S. F., et al. (2008). "New blood-based biomarkers for the diagnosis, staging and prognosis of prostate cancer." Bju International 101(6): 675-683.
The introduction of prostate-specific antigen (PSA) has revolutionized the detection and management of patients with prostate cancer. Despite this there has always been a concern among clinicians about the usefulness of total PSA levels as a marker for prostate cancer. We discuss the use of calculated variables and molecular forms of PSA. The precursor forms of PSA have been associated with the presence and biological behaviour of prostate cancer. With recent advances in biotechnology, e.g. high-throughput molecular analyses, many potential blood biomarkers have been identified and are currently under investigation. Given the plethora of candidate biomarkers we discuss a selected group of novel blood-based biomarkers, e.g. human glandular kallikrein, early prostate cancer antigen, insulin-like growth factors, urokinase plasminogen activators, transforming growth factor-beta, interleukin-6, chromogranin A, and prostate secretory protein. While these and other markers have shown promise in early-phase studies, no single biomarker is likely to have the appropriate degree of certainty to dictate treatment decisions. Consequently, the future of cancer prognosis might rely on small panels of markers that can accurately predict cancer presence, stage and metastasis, and serve as prognosticators, targets, and/or surrogate endpoints of disease progression and response to therapy.

Shimada, O., et al. (2007). "Human agonistic antibody to tumor necrosis factor-related apoptosis-inducing ligand receptor 2 induces cytotoxicity and apoptosis in prostate cancer and bladder cancer cells." Urology 69(2): 395-401.

OBJECTIVES Tumor necrosis factor-related apoptosis-inducing tigand (TRAIL) induces apoptosis in a variety of tumor cells through two of its receptors: TRAIL-RI and TRAIL-R2. In this study, we investigated the susceptibility of human prostate cancer and bladder cancer cells to HGS-ETR2, a human monoclonal agonistic antibody specific for TRAIL-R2. METHODS The cell surface expression of TRAIL-RI and TRAIL-R2 on prostate cancer and bladder cancer cells was determined using flow cytometry. Cytotoxicity was assessed by 3-(4,5-dimethylthiazot-2-yl)-2,5-diphenyltetrazolium bromide assay, and caspase activities were measured by a quantitative colorimetric assay. RESULTS HGS-ETR2 effectively induced apoptotic cell death in DU145, PC3, and LNCaP human prostate cancer cells and J82 and T24 human bladder cancer cells. The increased effectiveness of HGS-ETR2 for inducing cell death might have been affected by differences in the cell surface expression of the two TRAIL receptors, in that TRAIL-R2, but not TRAIL-RI, was frequently expressed in the prostate cancer and bladder cancer cells. HGS-ETR2 significantly activated the caspase cascade, including caspase-3, -6, -8, and -9, which were the downstream molecules of the death receptors in prostate cancer cells. Caspase-3, -6, and -9 were also significantly activated with HGS-ETR2-induced apoptosis in the bladder cancer cells. CONCLUSIONS These findings suggest the potential utility of TRAIL-R2 antibody as a novel therapeutic agent against prostate cancer and bladder cancer.

Simons, J. W. (2014). "Prostate Cancer Immunotherapy: Beyond Immunity to Curability." Cancer Immunology Research 2(11): 1034-1043.

Metastatic prostate cancer is the second leading cause of death from cancer in the United States. It is the first prevalent cancer in which overall survival in advanced disease is modestly, but objectively, improved with outpatient delivered dendritic cell-based immunotherapy. More prostate cancer patients have enrolled through Facebook and trusted-site Internet searches in clinical trials for prostate cancer vaccine-based immunotherapy than in immunotherapy trials for lung, breast, colon, pancreas, ovarian, and bladder cancer combined in the past 7 years. Exceptional responses to anti-CTLA-4 treatment have been documented in clinics, and prostate cancer neoantigen characterization and T-cell clonotyping are in their research ascendancy. The prostate is an accessory organ; it is not required for fertility, erectile function, or urinary continence. The true evolutionary advantage of having a prostate for male mammalian physiology is a topic of speculation in seminar rooms and on bar stools, but it remains unknown. Hundreds of prostate lineage-unique proteins (PLUP) exist among the >37,000 normal human prostate lineage-unique open reading frames that can be targeted for immunologic ablation of PLUP+ prostate cancer cells by prostate-specific autoimmunity. This bioengineered graft-versus-prostate disease is a powerful strategy that can eliminate deaths from prostate cancer. Immunologic tolerance to prostate cancer can be overcome at every clinical stage of presentation. This Cancer Immunology at the Crossroads article aims to present advances in the past two decades of basic, translational, and clinical research in prostate cancer, including bioengineering B-cell and T-cell responses, and ongoing prostate cancer immunotherapy trials. (C) 2014 AACR.

Sonpavde, G., et al. (2011). "GLIPR1 Tumor Suppressor Gene Expressed by Adenoviral Vector as Neoadjuvant Intraprostatic Injection for Localized Intermediate or High-Risk Prostate Cancer Preceding Radical Prostatectomy." Clinical Cancer Research 17(22): 7174-7182.

Background: GLIPR1 is upregulated by p53 in prostate cancer cells and has preclinical antitumor activity. A phase I clinical trial was conducted to evaluate the safety and activity of the neoadjuvant intraprostatic injection of GLIPR1 expressing adenovirus for intermediate or high-risk localized prostate cancer before radical prostatectomy (RP). Methods: Eligible men had localized prostate cancer (T1-T2c) with Gleason score greater than or equal to 7 or prostate-specific antigen 10 ng/mL or more and were candidates for RP. Patients received the adenoviral vector expressing the GLIPR1 gene by a single injection into the prostate followed four weeks later by RP. Six viral particle (vp) dose levels were evaluated: 10(10), 5 x 10(10), 10(11), 5 x 10(11), 10(12), and 5 x 10(12) vp. Results: Nineteen patients with a median age of 64 years were recruited. Nine men had T1c, 4 had T2a, and 3 had T2b and T2c clinical stage. Toxicities included urinary tract infection (n = 3), flu-like syndrome (n = 3), fever (n = 1), dysuria (n = 1), and photophobia (n = 1). Laboratory toxicities were grade 1 elevated AST/ALT (n = 1) and elevations of PTT (n = 3, with 1 proven to be lupus anticoagulant). No pathologic complete remission was seen. Morphologic cytotoxic activity, induction of apoptosis, and nuclear p27(Kip1) upregulation were observed. Peripheral blood CD8(+), CD4(+), and CD3(+) T-lymphocytes were increased, with upregulation of their HLA-DR expression and elevations of serum IL-12. Conclusions: The intraprostatic administration of GLIPR1 tumor suppressor gene expressed by an adenoviral vector was safe in men, with localized intermediate or high-risk prostate cancer preceding RP. Preliminary evidence of biologic antitumor activity and systemic immune response was documented.
Clin Cancer Res; 17(22); 7174-82. (C) 2011 AACR.

Sreekumar, A., et al. (2009). "Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression." Nature 457(7231): 910-914.

Multiple, complex molecular events characterize cancer development and progression(1,2). Deciphering the molecular networks that distinguish organ- confined disease from metastatic disease may lead to the identification of critical biomarkers for cancer invasion and disease aggressiveness. Although gene and protein expression have been extensively profiled in human tumours, little is known about the global metabolomic alterations that characterize neoplastic progression. Using a combination of high- throughput liquid- and gas- chromatography- based mass spectrometry, we profiled more than 1,126 metabolites across 262 clinical samples related to prostate cancer (42 tissues and 110 each of urine and plasma). These unbiased metabolomic profiles were able to distinguish benign prostate, clinically localized prostate cancer and metastatic disease. 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 and can be detected non-invasively in urine. Sarcosine levels were also increased in invasive prostate cancer cell lines relative to benign prostate epithelial cells. Knockdown of glycine- N- methyl transferase, the enzyme that generates sarcosine from glycine, attenuated prostate cancer invasion. Addition of exogenous sarcosine or knockdown of the enzyme that leads to sarcosine degradation, sarcosine dehydrogenase, induced an invasive phenotype in benign prostate epithelial cells. Androgen receptor and the ERG gene fusion product coordinately regulate components of the sarcosine pathway. Here, by profiling the metabolomic alterations of prostate cancer progression, we reveal sarcosine as a potentially important metabolic intermediary of cancer cell invasion and aggressivity.

Stephan, C., et al. (2013). "Comparative Assessment of Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG Gene Fusion with the Serum -2 Proprostate-Specific Antigen-Based Prostate Health Index for Detection of Prostate Cancer." Clinical Chemistry 59(1): 280-288.

BACKGROUND: We compared urinary prostate cancer antigen 3 (PCA3), transmembrane protease, serine 2 (TMPRSS2):v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG) gene fusion (T2:ERG), and the serum [-2]proprostate-specific antigen ([-2]proPSA)-based prostate health index (Phi) for predicting biopsy outcome. METHODS: Serum samples and first-catch urine samples were collected after digital rectal examination (DRE) from consented outpatients with PSA 0.5-20 mu g/L who were scheduled for prostate biopsy. The PCA3 score (PROGENSA PCA3, Hologic Gen-Probe) and T2:ERG score (Hologic Gen-Probe) were determined. Measurements of serum PSA, free PSA, and [-2]proPSA (Beckman Coulter) were performed, and the percentages of free PSA (%fPSA) and Phi ([-2]proPSA/fPSA X root PSA) were determined. RESULTS: Of 246 enrolled men, prostate cancer (PCa) was diagnosed in 110 (45%) and there was no evidence of malignancy (NEM) in 136 (55%). A first set of biopsies was performed in 136 (55%) of all men, and 110 (45%) had >= 1 repeat biopsies. PCA3, Phi, and T2:ERG differed significantly between men with PCa and NEM, and these markers showed the largest areas under the ROC curve (AUCs) (0.74, 0.68, and 0.63, respectively). PCA3 had the largest AUC of all parameters, albeit not statistically different from Phi. Phi showed somewhat lower specificities than PCA3 at 90% sensitivity. Combination of both markers enhanced diagnostic power with modest AUC gains of 0.01-0.04. Although PCA3 had the highest AUC in the repeat-biopsy cohort, the highest AUC for Phi was observed in DRE-negative patients with PSA in the 2-10 mu g/L range. CONCLUSIONS: PCA3 and Phi were superior to the other evaluated parameters but their combination gave only moderate enhancements in diagnostic accuracy for PCa at first or repeat prostate biopsy. (C) 2012 American Association for Clinical Chemistry

Stovsky, M., et al. (2011). "Prostate-specific Antigen/Solvent Interaction Analysis: A Preliminary Evaluation of a New Assay Concept for Detecting Prostate Cancer Using Urinary Samples." Urology 78(3): 601-605.

OBJECTIVE To provide preliminary clinical performance evaluation of a novel prostate cancer (CaP) assay, prostate-specific antigen/solvent interaction analysis (PSA/SIA) that focused on changes to the structure of PSA. METHODS Two-hundred twenty-two men undergoing prostate biopsy for accepted clinical criteria at 3 sites (University Hospitals Case Medical Center in Cleveland, Cleveland Clinic, and Veterans Administration Boston Healthcare System) were enrolled in institutional review board-approved study. Before transrectal ultrasound-guided biopsy, patients received digital rectal examination with systematic prostate massage followed by collection of urine. The PSA/SIA assay determined the relative partitioning of heterogeneous PSA isoform populations in urine between 2 aqueous phases. A structural index, K, whose numerical value is defined as the ratio of the concentration of all PSA isoforms, was determined by total PSA enzyme-linked immunosorbent assay and used to set a diagnostic threshold for CaP. Performance was assessed using receiver operating characteristic (ROC) analysis with biopsy as the gold standard. RESULTS Biopsies were pathologically classified as case (malignant, n = 100) or control (benign, n = 122). ROC performance demonstrated area under the curve = 0.90 for PSA/SIA and 0.58 for serum total PSA. At a cutoff value of k = 1.73, PSA/SIA displayed sensitivity = 100%, specificity = 80.3%, positive predictive value = 80.6%, and negative predictive value = 100%. No attempt was made in this preliminary study to further control patient population or selection criteria for biopsy, nor did we analytically investigate the type of structural differences in PSA that led to changes in k value. CONCLUSION PSA/SIA provides ratiometric information independently of PSA concentration. In this preliminary study, analysis of the overall structurally heterogeneous PSA isoform population using the SIA assay showed promising results to be further evaluated in future studies. UROLOGY 78: 601-606, 2011. (C) 2011 Elsevier Inc. All rights reserved.

Strittmatter, F., et al. (2011). "Alpha1-adrenoceptor Signaling in the Human Prostate Involves Regulation of p38 Mitogen-activated Protein Kinase." Urology 78(4).

OBJECTIVE To investigate whether 1-adrenoceptor signaling in the human prostate involves regulation of the mitogen-activated protein kinase (MAPK) p38. Although alpha 1-adrenoceptors are an important target for therapy of lower urinary tract symptoms in patients with prostate hyperplasia, intracellular signaling by prostate alpha 1-adrenoceptors is not sufficiently understood. METHODS Prostate tissue was obtained from patients undergoing radical prostatectomy. The effect of phenylephrine (10 mu M) on p38 activity was assessed by Western blot analysis with a phosphospecific antibody. Expression of p38 was studied by immunohistochemistry and immunofluorescence staining. The effect of the p38 inhibitor SB 202190 (10 mu M) on phenylephrine-induced contraction was studied in myographic measurements. RESULTS Stimulation of human prostate tissue with phenylephrine resulted in reduced threonine180/tyrosine182 phosphorylation of p38, indicating deactivation of p38 (P = .039 after 5 minutes). Immunohistochemical staining demonstrated expression of p38 in stromal cells of human prostate tissue. Immunofluorescence staining identified these cells as smooth muscle cells, as p38 colocalized with immunoreactivity for alpha-smooth muscle actin. The p38 inhibitor SB 202190 was without effect on phenylephrine-induced contraction. CONCLUSION Using intact human prostate tissue, we herewith describe a new signal transduction pathway of prostate alpha 1-adrenoceptors. In addition to mediating contraction, prostate alpha 1-adrenoceptors induce intracellular signaling, which results in deactivation of p38 MAPK. This is not involved in alpha 1-adrenergic contraction, and points to alpha 1-adrenoceptor functions beyond contraction. UROLOGY 78: 969.e7-969.e13, 2011. (C) 2011 Elsevier Inc.

Strittmatter, F., et al. (2012). "Inhibition of adrenergic human prostate smooth muscle contraction by the inhibitors of c-Jun N-terminal kinase, SP600125 and BI-78D3." British Journal of Pharmacology 166(6): 1926-1935.

BACKGROUND AND PURPOSE a1-Adrenoceptor-induced contraction of prostate smooth muscle is mediated by calcium- and Rho kinase-dependent mechanisms. In addition, other mechanisms, such as activation of c-jun N-terminal kinase (JNK) may be involved. Here, we investigated whether JNK participates in a1-adrenoceptor-induced contraction of human prostate smooth muscle. EXPERIMENTAL APPROACH Prostate tissue was obtained from patients undergoing radical prostatectomy. Effects of the JNK inhibitors SP600125 (50 mu M) and BI-78D3 (30 mu M) on contractions induced by phenylephrine, noradrenaline and electric field stimulation (EFS) were studied in myographic measurements. JNK activation by noradrenaline (30 mu M) and phenylephrine (10 mu M), and the effects of JNK inhibitors of c-Jun phosphorylation were assessed by Western blot analyses with phospho-specific antibodies. Expression of JNK was studied by immunohistochemistry and fluorescence double staining. KEY RESULTS The JNK inhibitors SP600125 and BI-78D3 reduced phenylephrine- and noradrenaline-induced contractions of human prostate strips. In addition, SP600125 reduced EFS-induced contraction of prostate strips. Stimulation of prostate tissue with noradrenaline or phenylephrine in vitro resulted in activation of JNK. Incubation of prostate tissue with SP600125 or BI-78D3 reduced the phosphorylation state of c-Jun. Immunohistochemical staining demonstrated the expression of JNK in smooth muscle cells of human prostate tissue. Fluorescence staining showed that a1A-adrenoceptors and JNK are expressed in the same cells. CONCLUSIONS AND IMPLICATIONS Activation of JNK is involved in a1-adrenoceptor-induced prostate smooth muscle contraction. Models of a1-adrenoceptor-mediated prostate smooth muscle contraction should include this JNK-dependent mechanism.

Strittmatter, F., et al. (2012). "Activation of protein kinase B/Akt by alpha1-adrenoceptors in the human prostate." Life Sciences 90(11-12): 446-453.

Aims: Besides their role in contraction, alpha 1-adrenoceptors may be involved in prostate hyperplasia. This would require receptor signaling by growth-promoting pathways. Akt (syn. Protein kinase B) is an important regulator of growth and differentiation. Objective: To investigate whether alpha 1-adrenoceptors in the human prostate activate Akt. Main methods: Prostate tissue was obtained from patients undergoing radical prostatectomy. Akt expression was investigated by RT-PCR. Western blot, and immunohistochemistry. Akt activation by noradrenaline (30 mu M) and phenylephrine (10 mu M) was assessed by Western blot analyses with a phospho-specific antibody. The effects of the Akt inhibitors FPA-124 and 10-DEBC on phenylephrine-, noradrenaline- and electric field stimulation- (EFS-) induced contraction were studied in myographic measurements. Key findings: mRNA of all three Akt isoforms (Akt1, Akt2, Akt3) was detected by RT-PCR in all prostate samples (n = 6 patients). Protein expression was confirmed by Western blot analysis (n = 8 patients). Immunohistochemical staining for Akt revealed strong immunoreactivity in prostate smooth muscle cells (n = 5 patients). Stimulation of prostate tissues with noradrenaline (30 mu M, n = 8 patients) or phenylephrine (10 mu M, n=7 patients) caused significant Akt phosphorylation at serine-473, indicating activation of Akt. FPA124 and 10-DEBC were without effects on noradrenaline-, phenylephrine-, or EFS-induced contraction of prostate strips. Significance: Prostate alpha 1-adrenoceptors activate Akt. Consequently, Akt is a target of alpha 1-blocker therapy, which has been unknown to date. Our findings point to functions of prostate alpha 1-adrenoceptors besides contraction. (C) 2012 Elsevier Inc. All rights reserved.

Suga, T., et al. (2008). "Influence of multiple genetic polymorphisms on genitourinary morbidity after carbon ion radiotherapy for prostate cancer." International Journal of Radiation Oncology Biology Physics 72(3): 808-813.

Purpose: To investigate the genetic risk of late urinary morbidity after carbon ion radiotherapy in prostate cancer patients. Methods and Materials: A total of 197 prostate cancer patients who had undergone carbon ion radiotherapy were evaluated for urinary morbidity. The distribution of patients with dysuria was as follows: Grade 0, 165; Grade 1, 28; and Grade 2, 4 patients. The patients were divided (2: 1) consecutively into the training and test sets and then categorized into control (Grade 0) and case (Grade I or greater) groups. First, 450 single nucleotide polymorphisms (SNPs) in 118 candidate genes were genotyped in the training set. The associations between the SNP genotypes and urinary morbidity were assessed using Fisher's exact test. Then, various combinations of the markers were tested for their ability to maximize the area under the receiver operating characteristics (AUC-ROC) curve analysis results. Finally, the test set,vas validated for the selected markers. Results: When the SNP markers in the SART1, ID3. EPDR1, PAH, and XRCC6 genes in the training set were subjected to AUC-ROC curve analysis, the AUC-ROC curve reached a maximum of 0.86. The AUC-ROC curve of these markers in the test set was 0.77. The SNPs in these five genes were defined as "risk genotypes." Approximately 90% of patients in the case group (Grade 1 or greater) had three or more risk genotypes. Conclusions: Our results have shown that patients with late urinary morbidity after carbon ion radiotherapy can be stratified according to the total number of risk genotypes they harbor. (C) 2008 Elsevier Inc.

Supiot, S., et al. (2008). "A phase I trial of pre-operative radiotherapy for prostate cancer: Clinical and translational studies." Radiotherapy and Oncology 88(1): 53-60.

Background and purpose: Selected patients undergoing radical prostatectomy for localized prostate cancer can be at high-risk for pT3 disease and require subsequent radiotherapy. In a phase I trial, we investigated the feasibility of preoperative radiotherapy for this patient subset. Materials and methods: Eligibility criteria were: T1/T2N0M0 tumors plus (i) Gleason >= 7, PSA > 10 ng/ml and < 35 ng/ml or (ii), PSA > 15 ng/ml and less < 35 ng/ml (any Gleason). Patients received 25 Gy in five fractions of radiotherapy followed by radical prostatectomy. Trial endpoints included intra-operative morbidity and late toxicity following combined treatment. We also stained pre- and post-radiotherapy prostate samples for DNA damage response proteins. Results: Between 2001 and 2004, 15 patients were entered on trial. Thirteen patients completed combined-modality treatment. Only one patient had signs of intra-operative inflammation. No patient had post-operative complication. There was no severe late gastrointestinal toxicity. Late genitourinary toxicity consisted of severe urinary incontinence in 2 of 13 patients. From a translational standpoint, irradiated prostate tumor tissues had long-term activation of the CDK-inhibitor p21(WAF) associated with reduced cell proliferation. Conclusion: Intra-operative morbidity is low following short-course, pre-operative radiotherapy. A phase II trial is planned to fully document biochemical response with this combined-modality approach. (c) 2008 Elsevier Ireland Ltd. All rights reserved.

Takahashi, R. H., et al. (2012). "An intrapelvic extraintestinal gastrointestinal stromal tumor of undetermined origin: Diagnosis by prostate needle biopsy." Pathology Research and Practice 208(12): 736-740.

We herein report a case of intrapelvic gastrointestinal stromal tumor (GIST) of undetermined origin in a 48-year-old male who presented with dysuria. An enlarged tumor was detected on digital rectal examination. Imaging studies showed a solid and lobular homogenous tumor of 7.0 cm in diameter. The tumor was attached to the right dorsal aspect of the prostate with compression of the seminal vesicles and rectum. It was considered that the tumor had arisen from the prostate, although the patient's serum prostate-specific antigen level was low (0.436 ng/mL). The histological diagnosis by prostate needle biopsy was a spindle cell tumor. At cystoprostatectomy, the tumor was confirmed to be separated from the prostate by a fibrous band, and showed spindle cells with a fascicular growth pattern, but without necrotic areas. Mitotic figures were noted in 12 of 50 high-power fields. The tumor cells were immunoreactive for the KIT protein (CD117), CD34, Discovered on GIST-1 (DOG-1), and vimentin. In contrast, they were negative for desmin, alpha-smooth muscle actin, pancytokeratin (AE1/AE3), and S100 protein. The Ki-67 labeling index was 5%. The genetic analyses targeting the c-kit gene revealed a point mutation at codon 559 (GTT -> GAT). The diagnosis of GIST was confirmed on the basis of the morphological features, immuno-profile, and results of the molecular analyses. Since extraintestinal GIST can resemble a prostatic tumor clinically, KIT (CD117) and DOG-1 should be considered for inclusion in the immunohistochemical panel for spindle cell tumors obtained by prostate needle biopsy. (c) 2012 Elsevier GmbH. All rights reserved.

Tallon, L., et al. (2014). "Comparative Evaluation of Urinary PCA3 and TMPRSS2: ERG Scores and Serum PHI in Predicting Prostate Cancer Aggressiveness." International Journal of Molecular Sciences 15(8): 13299-13316.

It has been suggested that urinary PCA3 and TMPRSS2: ERG fusion tests and serum PHI correlate to cancer aggressiveness-related pathological criteria at prostatectomy. To evaluate and compare their ability in predicting prostate cancer aggressiveness, PHI and urinary PCA3 and TMPRSS2: ERG (T2) scores were assessed in 154 patients who underwent radical prostatectomy for biopsy-proven prostate cancer. Univariate and multivariate analyses using logistic regression and decision curve analyses were performed. All three markers were predictors of a tumor volume >= 0.5 mL. Only PHI predicted Gleason score >= 7. T2 score and PHI were both independent predictors of extracapsular extension (>= pT3), while multifocality was only predicted by PCA3 score. Moreover, when compared to a base model (age, digital rectal examination, serum PSA, and Gleason sum at biopsy), the addition of both PCA3 score and PHI to the base model induced a significant increase (+12%) when predicting tumor volume >0.5 mL. PHI and urinary PCA3 and T2 scores can be considered as complementary predictors of cancer aggressiveness at prostatectomy.

Taneja, S. S. (2014). "Re: urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the canary prostate active surveillance study." The Journal of urology 191(1): 75-76.

Tang, Y.-Q., et al. (2013). "Phyllanthus Suppresses Prostate Cancer Cell, PC-3, Proliferation and Induces Apoptosis through Multiple Signalling Pathways (MAPKs, PI3K/Akt, NF kappa B, and Hypoxia)." Evidence-Based Complementary and Alternative Medicine.

Phyllanthus is a traditional medicinal plant that has been found to have antihepatitis, antibacterial, and anticancer properties. The present studies were to investigate the in vitro molecular mechanisms of anticancer effects of Phyllanthus (P. amarus, P. niruri, P. urinaria, and P. watsonii) plant extracts in human prostate adenocarcinoma. The cancer ten-pathway reporter array was performed and revealed that the expression of six pathway reporters were significantly decreased (Wnt, NF kappa B, Myc/Max, hypoxia, MAPK/ERK, and MAPK/JNK) in PC-3 cells after treatment with Phyllanthus extracts. Western blot was conducted and identified several signalling molecules that were affected in the signalling pathways including pan-Ras, c-Raf, RSK, Elk1, c-Jun, JNK1/2, p38 MAPK, c-myc, DSH, beta-catenin, Akt, HIF-1 alpha, GSK3 beta, NF kappa B p50 and p52, Bcl-2, Bax, and VEGF, in treated PC-3 cells. A proteomics-based approach, 2D gel electrophoresis, was performed, and mass spectrometry (MS/MS) results revealed that there were 72 differentially expressed proteins identified in treated PC-3 cells and were involved in tumour cell adhesion, apoptosis, glycogenesis and glycolysis, metastasis, angiogenesis, and protein synthesis and energy metabolism. Overall, these findings suggest that Phyllanthus can interfere with multiple signalling cascades involved in tumorigenesis and be used as a potential therapeutic candidate for treatment of cancer.

Tang, Y.-Q., et al. (2013). "Phyllanthus Suppresses Prostate Cancer Cell, PC-3, Proliferation and Induces Apoptosis through Multiple Signalling Pathways (MAPKs, PI3K/Akt, NFkappaB, and Hypoxia)." Evidence-based complementary and alternative medicine : eCAM 2013: 609581-609581.

Tavukcu, H. H., et al. (2013). "Preliminary Results of Noninvasive Detection of TMPRSS2:ERG Gene Fusion in a Cohort of Patients With Localized Prostate Cancer." Korean journal of urology 54(6): 359-363.

PURPOSE: The aim of this study was to evaluate TMPRSS2:ERG fusion rates in tissue, urine, blood, and pubic hair samples in a cohort of patients with localized prostate cancer and to correlate these findings with various clinicopathological parameters. MATERIALS AND METHODS: A cohort of 40 patients undergoing radical prostatectomy for localized prostate cancer (RRP group) and 10 control patients undergoing prostate biopsy were enrolled between 2006 and 2008. Urine, pubic hair, and peripheral blood samples were obtained following prostatic massage before the needle biopsy or radical prostatectomy. Quantitative polymerase chain reaction analysis was performed on all collected samples. RESULTS: The patients' mean age was 62.4 (±5.5) years. We observed higher expressions of TMPRSS2:ERG fusion in tissue, urine, and blood samples from the RRP group than in samples from the control group. Overall, the fusion was present in urine samples of 23 RRP patients (57.5%). To predict high-stage cancer (>T3a), the Gleason score was the only significant factor in the logistic regression analysis (score, 10.579; p=0.001). Quantitative evaluation of the gene fusion in tissue (Pearson r=0.36, p=0.011) and urine (Pearson r=0.34, p=0.014) samples had a significant positive correlation with the preoperative prostate-specific antigen level. CONCLUSIONS: Urine sediments collected after prostatic massage appear to be a feasible noninvasive method of detecting TMPRSS2:ERG fusion. The Gleason score is the only significant factor to predict high-stage cancer (>T3a). No correlation between TMPRSS2:ERG gene fusion status and tumor stage, Gleason grade, prostate-specific antigen level, or surgical margin status was observed.

Thorsen, K., et al. (2008). "Alternative splicing in colon, bladder, and prostate cancer identified by exon array analysis." Molecular & Cellular Proteomics 7(7): 1214-1224.
Alternative splicing enhances proteome diversity and modulates cancer-associated proteins. To identify tissue- and tumor-specific alternative splicing, we used the GeneChip Human Exon 1.0 ST Array to measure whole-genome exon expression in 102 normal and cancer tissue samples of different stages from colon, urinary bladder, and prostate. We identified 2069 candidate alternative splicing events between normal tissue samples from colon, bladder, and prostate and selected 15 splicing events for RT-PCR validation, 10 of which were successfully validated by RT-PCR and sequencing. Furthermore 23, 19, and 18 candidate tumor-specific splicing alterations in colon, bladder, and prostate, respectively, were selected for RT-PCR validation on an independent set of 81 normal and tumor tissue samples. In total, seven genes with tumor-specific splice variants were identified (ACTN1, CALD1, COL6A3, LRRFIP2, PIK4CB, TPM1, and VCL). The validated tumor-specific splicing alterations were highly consistent, enabling clear separation of normal and cancer samples and in some cases even of different tumor stages. A subset of the tumor-specific splicing alterations (ACTN1, CALD1, and VCL) was found in all three organs and may represent general cancer-related splicing events. In silico protein predictions suggest that the identified cancers-pecific splice variants encode proteins with potentially altered functions, indicating that they may be involved in pathogenesis and hence represent novel therapeutic targets. In conclusion, we identified and validated alternative splicing between normal tissue samples from colon, bladder, and prostate in addition to cancer-specific splicing events in colon, bladder, and prostate cancer that may have diagnostic and prognostic implications.

Thurner, E. M., et al. (2014). "Association of genetic variants in apoptosis genes FAS and FASL with radiation-induced late toxicity after prostate cancer radiotherapy." Strahlentherapie Und Onkologie 190(3): 304-309.

Fas ligand (FASL) triggers apoptotic cell death by cross-linking with its receptor FAS, and after irradiation, expression of FAS and FASL is increased. In the present study, we investigated the association between common polymorphisms in the genes for FAS and FASL and the risk of late side effects after radiotherapy for prostate cancer. The role of FAS (-aEuro parts per thousand 1377G > A, rs2234767 and -aEuro parts per thousand 670A > G, rs1800682) and FASL (-aEuro parts per thousand 844C > T, rs763110) gene polymorphisms in the development of high-grade late rectal and/or urinary toxicity (defined as late toxicity EORTC/RTOG grade a parts per thousand yenaEuro parts per thousand 2) was analyzed in 607 prostate cancer patients treated with radiotherapy. DNA was isolated and the selected polymorphisms were determined by 5'-nuclease (TaqMan) assays. After a median follow-up time of 82 months, high-grade late rectal and/or urinary toxicity was observed in 175 patients (29.7 %). Univariate analysis revealed a significantly decreased risk of high-grade late toxicity in carriers of the FASL -aEuro parts per thousand 844T allele. After adjusting for covariates, patients harboring at least one -aEuro parts per thousand 844T allele (CT or TT genotype) remained at decreased risk of high-grade late toxicity compared with patients harboring the CC genotype [hazard ratio (HR) 0.585, 95 %CI 0.39-0.878; p = 0.010]. For patients with the -aEuro parts per thousand 844TT genotype, the HR was 0.404 (95 %CI 0.171-0.956; p = 0.039) in multivariate analysis. No significant associations were found for the remaining polymorphisms analyzed. These results provide the first evidence that the presence of the FASL -aEuro parts per thousand 844T variant allele may have a protective effect against the development of high-grade late rectal and/or urinary side effects after prostate cancer radiotherapy.

Tischkowatz, M. D., et al. (2008). "Identification and characterization of novel SNPs in CHEK2 in Ashkenazi Jewish men with prostate cancer." Cancer Letters 270(1): 173-180.
Checkpoint kinase 2 (CHEK2) is a protein involved in arresting cell cycle in response to DNA damage. To investigate whether it plays an important role in the development of prostate cancer (PRCA) in the Ashkenazi Jewish (AJ) population, we sequenced CHEK2 in 75 AJ individuals with prostate, breast, or no cancer (n = 25 each). We identified seven coding SNPs (five are novel) that changed the amino-acid sequence, resulting in R3W, E394F, Y424H, S428F, D438Y, P509S, and P509L. We determined the frequency of each variant in 76 AJ families collected by members of the International Consortium for Prostate Cancer Genetics (ICPCG) where >= 2 men were affected by PRCA. Only one variant, Y424H in exon 11, was identified in more than two families. Exon 11 was then screened in nine additional AJ ICPCG families (a total of 85 families). The Y424H variant occurred in nine affected cases from four different families; however, it did not completely segregate with the disease. We performed bioinformatics analysis, which showed that Y424H is a non-conservative missense substitution that falls at a position that is invariant in vertebrate CHEK2 orthologs. Both SIFT and Align-GVGD predict that Y424H is a loss of function mutation. However, the frequency of Y424H was not significantly different between unselected AJ cases from Montreal/Memorial Sloan Kettering Cancer Centre (MSKCC) and AJ controls from Israel/MSKCC (OR 1.18, 95%CI: 0.34-4.61, p=.99). Moreover, functional assays using Saccharomyces cerevisiae revealed that the Y424H substitution did not alter function of CHEK2 protein. Although we cannot rule out a subtle influence of the CHEK2 variants on PRCA risk, these results suggest that germline CHEK2 mutations have a minor role in, if any, PRCA susceptibility in AJ men. (c) 2008 Elsevier Ireland Ltd. All rights reserved.

Toelle, A., et al. (2011). "Fatty acid binding proteins (FABPs) in prostate, bladder and kidney cancer cell lines and the use of IL-FABP as survival predictor in patients with renal cell carcinoma." Bmc Cancer 11.

Background: Fatty acid binding proteins (FABP) play an important role in carcinogenesis. Modified FABP expression patterns were described for prostate, bladder and for renal cell carcinoma. Studies on metabolic relationships and interactions in permanent cell lines allow a deeper insight into molecular processes. The aim of this study is therefore a systematic overview on mRNA and protein expressions of seven FABPs in frequently used urological cell lines. Methods: Nine cell lines of renal carcinomas, seven of urinary bladder carcinomas, and five of prostate carcinomas were investigated. Quantitative RT-qPCR and western blotting were used to determine different FABPs. In addition, 46 paired cancerous and noncancerous tissue samples from nephrectomy specimen with renal cell carcinomas were investigated regarding the ileum FABP mRNA expression level and associated with survival outcome. Results: General characteristics of all urological carcinoma cell lines were the expression of E-and IL-FABP on mRNA and protein level, while the expressions differed between the cell lines. The protein expression was not always congruent with the mRNA expression. Renal cell carcinoma cell lines showed expressions of L-, H- and B-FABP mRNA in addition to the general FABP expression in five out of the eight investigated cell lines. In bladder cancer cell lines, we additionally found the expression of A-FABP mRNA in six cell lines, while H-FABP was present only in three cell lines. In prostate cancer cell lines, a strong reduction of A-and E-FABP mRNA was observed. The expression of B-FABP mRNA and protein was observed only in the 22 RV-1 cells. IL-FABP mRNA was over-expressed in renal tumour tissue. The IL-FABP ratio was identified as an independent indicator of survival outcome. Conclusions: Distinctly different FABP expression patterns were observed not only between the cell lines derived from the three cancer types, but also between the cell lines from the same cancer. The FABP patterns in the cell lines do not always reflect the real situation in the tumours. These facts have to be considered in functional studies concerning the different FABPs.

Toffolatti, L., et al. (2006). "Expression analysis of androgen-responsive genes in the prostate of veal calves treated with anabolic hormones." Domestic Animal Endocrinology 30(1): 38-55.

In order to identify indirect molecular biomarkers of anabolic treatments in veal calves, an animal experiment was performed using two combinations of growth promoters (consisting of boldenone undecylenate and estradiol benzoate, and of testosterone enantate and estradiol benzoate). We selected a set of 12 genes that are known to be androgen responsive in other mammalian species. The expression profile of this set of genes was analysed on prostate samples of veal calves using a real-time RTPCR approach. For each selected gene the corresponding bovine sequence was obtained and a gene specific real-time assay was optimised and validated. The amplification was shown to be highly specific, linear and efficient. High reproducibility (< 1%) and low-test variability (< 2.5%) were also been achieved. Messenger RNA levels were quantified in prostate samples, non-parametric analysis of variance showed significant up-regulation of three genes (MAF, ESR1 and AR) and significant down-regulation of four genes (HMGCS 1, HPGD, DBI, and LIM) in treated samples when compared with untreated controls. To assess the possibility of identifying hormone-treated animals by molecular means we performed a discriminant analysis that was effective in classifying treated and non-treated samples with an accuracy of 93%. Our results indicate that identification of treatment with steroid hormones in veal calves by means of gene expression analysis is a feasible approach and could be improved increasing both the number of genes and the number of controls analysed. (c) 2005 Elsevier Inc. All rights reserved.

Tomlins, S. A., et al. (2011). "Urine TMPRSS2:ERG Fusion Transcript Stratifies Prostate Cancer Risk in Men with Elevated Serum PSA." Science Translational Medicine 3(94).

More than 1,000,000 men undergo prostate biopsy each year in the United States, most for "elevated" serum prostate-specific antigen (PSA). Given the lack of specificity and unclear mortality benefit of PSA testing, methods to individualize management of elevated PSA are needed. Greater than 50% of PSA-screened prostate cancers harbor fusions between the transmembrane protease, serine 2 (TMPRSS2) and v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG) genes. Here, we report a clinical-grade, transcription-mediated amplification assay to risk stratify and detect prostate cancer noninvasively in urine. The TMPRSS2: ERG fusion transcript was quantitatively measured in prospectively collected whole urine from 1312 men at multiple centers. Urine TMPRSS2: ERG was associated with indicators of clinically significant cancer at biopsy and prostatectomy, including tumor size, high Gleason score at prostatectomy, and upgrading of Gleason grade at prostatectomy. TMPRSS2: ERG, in combination with urine prostate cancer antigen 3 (PCA3), improved the performance of the multivariate Prostate Cancer Prevention Trial risk calculator in predicting cancer on biopsy. In the biopsy cohorts, men in the highest and lowest of three TMPRSS2: ERG+PCA3 score groups had markedly different rates of cancer, clinically significant cancer by Epstein criteria, and high-grade cancer on biopsy. Our results demonstrate that urine TMPRSS2: ERG, in combination with urine PCA3, enhances the utility of serum PSA for predicting prostate cancer risk and clinically relevant cancer on biopsy.

Tomlins, S. A., et al. (2009). "ETS Gene Fusions in Prostate Cancer: From Discovery to Daily Clinical Practice." European Urology 56(2): 275-286.
Context. In 2005, fusions between the androgen-regulated transmembrane protease serine 2 gene, TMPRSS2, and E twenty-six (ETS) transcription factors were discovered in prostate cancer. Objective: To review advances in our understanding of ETS gene fusions, focusing on challenges affecting translation to clinical application. Evidence acquisition: The PubMed database was searched for reports on ETS fusions in prostate cancer. Evidence synthesis: Since the discovery of ETS fusions, novel 5' and 3' fusion partners and multiple splice isoforms have been reported. The most common fusion, TMPRSS2:ERG, is present in approximately 50% of prostate-specific antigen (PSA)-screened localized prostate cancers and in 15-35% of population-based cohorts. ETS fusions can be detected noninvasively in the urine of men with prostate cancer, with a specificity rate in PSA-screened cohorts of >90%. Reports from untreated population-based cohorts suggest an association between ETS fusions and cancer-specific death and metastatic spread. In retrospective prostatectomy cohorts, conflicting results have been published regarding associations between ETS fusions and cancer aggressiveness. In addition to serving as a potential biomarker, tissue and functional studies suggest a specific role for ETS fusions in the transition to carcinoma. Finally, recent results suggest that the 5' and 3' ends of ETS fusions as well as downstream targets may be targeted therapeutically. Conclusions: Recent studies suggest that the first clinical applications of ETS fusions are likely to be in noninvasive detection of prostate cancer and in aiding with difficult diagnostic cases. Additional studies are needed to clarify the association between gene fusions and cancer aggressiveness, particularly those studies that take into account the multifocal and heterogeneous nature of localized prostate cancer. Multiple promising strategies have been identified to potentially target ETS fusions. Together, these results suggest that ETS fusions will affect multiple aspects of prostate cancer diagnosis and management. (C) 2009 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Tomlins, S. A., et al. (2008). "The role of SPINK1 in ETS rearrangement-negative prostate cancers." Cancer Cell 13(6): 519-528.
ETS gene fusions have been characterized in a majority of prostate cancers; however, the key molecular alterations in ETS-negative cancers are unclear. Here we used an outlier meta-analysis (meta-COPA) to identify SPINK1 outlier expression exclusively in a subset of ETS rearrangement-negative cancers (similar to 10% of total cases). We validated the mutual exclusivity of SPINK1 expression and ETS fusion status, demonstrated that SPINK1 outlier expression can be detected noninvasively in urine, and observed that SPINK1 outlier expression is an independent predictor of biochemical recurrence after resection. We identified the aggressive 22RV1 cell line as a SPINK1 outlier expression model and demonstrate that SPINK1 knockdown in 22RV1 attenuates invasion, suggesting a functional role in ETS rearrangement-negative prostate cancers.

Townes, C. L., et al. (2013). "Prostate specific antigen enhances the innate defence of prostatic epithelium against Escherichia coli infection." Prostate 73(14): 1529-1537.

BACKGROUND. This study investigated whether the increase in serum prostate specific antigen (PSA) typically seen during male urinary tract infection (UTI) is incidental or reflects an innate defence mechanism of the prostate. The protective roles of the whey-acid-motif-4-disulphide core (WFDC) proteins, secretory leukoproteinase inhibitor (SLPI) and WFDC2, in the prostate were also examined. METHODS. UTI recurrence was assessed retrospectively in men following initial UTI by patient interview. PSA, SLPI, and WFDC2 gene expression were assessed using biopsy samples. LNCaP and DU145 in vitro prostate cell models were utilized to assess the effects of an Escherichia coli challenge on PSA and WFDC gene expression, and bacterial invasion of the prostate epithelium. The effects of PSA on WFDC antimicrobial properties were studied using recombinant peptides and time-kill assays. RESULTS. Men presenting with PSA>4ng/ml at initial UTI were less likely to have recurrent (r) UTI than those with PSA<4ng/ml [2/15 (13%) vs. 7/10 (70%), P<0.01]. Genes encoding PSA, SLPI and WFDC2, were expressed in prostatic epithelium, and the PSA and SLPI proteins co-localized in vivo. Challenging LNCaP (PSA-positive) cells with E. coli increased PSA, SLPI, and WFDC2 gene expression (P<0.05), and PSA synthesis (P<0.05), and reduced bacterial invasion. Pre-incubation of DU145 (PSA-negative) cells with PSA also decreased bacterial invasion. In vitro incubation of recombinant SLPI and WFDC2 with PSA resulted in peptide proteolysis and increased E. coli killing. CONCLUSIONS. Increased PSA during UTI appears protective against rUTI and in vitro is linked to proteolysis of WFDC proteins supporting enhanced prostate innate defences. Prostate 73: 1529-1537, 2013. (c) 2013 Wiley Periodicals, Inc.

Trock, B. J. (2011). "Application of metabolomics to prostate cancer." Urologic Oncology-Seminars and Original Investigations 29(5): 572-581.

The prostate has long been known to exhibit unique metabolite profiles. In the last decade, advances in nuclear magnetic resonance spectroscopy and mass spectrometry have been applied toward identifying metabolic alterations in prostate cancer that may provide clinically useful biomarkers. As with genomics and proteomics, advances in technology and bioinformatics have led to the application of metabolomic profiling to prostate cancer the high throughput evaluation of a large complement of metabolites in the prostate and how they are altered by disease perturbations. Recently, high profile publications have drawn attention to the potential of metabolomic analysis to identify biomarkers for early detection or disease progression from readily accessible body fluids as well as tissue specimens from biopsy and surgery. This review will examine applications of metabolomics to prostate cancer and highlight clinical associations and potential challenges. (C) 2011 Elsevier Inc. All rights reserved.

True, L. D., et al. (2010). "CD90/THY1 is overexpressed in prostate cancer-associated fibroblasts and could serve as a cancer biomarker." Modern Pathology 23(10): 1346-1356.

A by-product in the processing of prostate tissue for cell sorting by collagenase digestion is the media supernatant that remains after the cells are harvested. These supernatants contain proteins made by the cells within the tissue. Quantitative proteomic analysis of N-glycosylated proteins detected an increased amount of CD90/THY1 in cancer supernatants compared with non-cancer supernatants. Immunohistochemistry showed that in all carcinomas, regardless of Gleason grade, a layer of CD90-positive stromal fibroblastic cells, similar to 5 to 10 cells deep, was localized to tumor glands. In contrast, a no more than 1-cell wide girth of CD90-positive stromal cells was found around benign glands. The increased number of CD90-positive stromal cells in cancer correlated with overexpression of CD90 mRNA detected by gene expression analysis of stromal cells obtained by laser-capture microdissection. There is increasing evidence that cancer-associated stroma has a function in both tumor progression and carcinogenesis. Most experiments to identify cancer biomarkers have focused on the cancer cells. CD90, being a marker for prostate cancer-associated stroma, might be a potential biomarker for this cancer. A non-invasive test could be provided by a urine test. Proteomic analysis of urine from patients with prostate cancer identified CD90; conversely, CD90 was not detected in the urine of post-prostatectomy patients. Furthermore, this urinary CD90 protein was a variant CD90 protein not known to be expressed by such cells as lymphocytes that express CD90. These CD90 results were obtained from similar to 90 cases consisting of proteomic analysis of tissue and urine, immunohistochemistry, western blot analysis of tissue media, flow cytometry of cells from digested tissue, and reverse transcriptase polymerase chain reaction analysis of isolated stromal cells. Modern Pathology (2010) 23, 1346-1356; doi:10.1038/modpathol.2010.122; published online 18 June 2010

Tsaur, I., et al. (2015). "CCL2 Chemokine as a Potential Biomarker for Prostate Cancer: A Pilot Study." Cancer Research and Treatment 47(2): 306-312.

Purpose Prostate specific antigen is not reliable in diagnosing prostate cancer (PCa), making the identification of novel, precise diagnostic biomarkers important. Since chemokines are associated with more aggressive disease and poor prognosis in diverse malignancies, we aimed to investigate the diagnostic relevance of chemokines in PCa. Materials and Methods Preoperative and early postoperative serum samples were obtained from 39 consecutive PCa patients undergoing radical prostatectomy. Serum from 15 healthy volunteers served as controls. Concentrations of CXCL12, CXCL13, CX3CL1, CCL2, CCL5, and CCL20 were measured in serum by Luminex. The expression activity of CXCR3, CXCR4, CXCR5, CXCR7, CXCL12, CXCL13, CX3CR1, CXCL1, CCR2, CCR5, CCR6, CCR7, CCL2, and CCL5 mRNA was assessed in tumor and adjacent normal tissue of prostatectomy specimens by quantitative real-time polymerase chain reaction. The associations of these chemokines with clinical and histological parameters were tested. Results The gene expression activity of CCL2 and CCR6 was significantly higher in tumor tissue compared to adjacent normal tissue. CCL2 was also significantly higher in the blood samples of PCa patients, compared to controls. CCL5, CCL20, and CX3CL1 were lower in patient serum, compared to controls. CCR2 tissue mRNA was negatively correlated with the Gleason score and grading. Conclusion Chemokines are significantly modified during tumorigenesis of PCa, and CCL2 is a promising diagnostic biomarker.

Tucci, M., et al. (2009). "Prognostic significance of disordered calcium metabolism in hormone-refractory prostate cancer patients with metastatic bone disease." Prostate Cancer and Prostatic Diseases 12(1): 94-99.

Bone metabolic disruption that occurs in bone metastatic prostate cancer could lead to disturbances of calcium metabolism. The prognostic role of either hypocalcemia or hypercalcemia was assessed in a consecutive series of hormone-refractory bone metastatic prostate cancer patients. Serum calcium was measured in 192 patients. The presence of hypocalcemia and hypercalcemia was related with baseline biochemical and clinical characteristics and the role of these two calcium disturbances in predicting prognosis and adverse skeletal-related events (SREs) was assessed. As compared to normocalcemic patients, hypocalcemic patients (n = 51) had higher tumor load in bone (P = 0.005), higher plasma chromogranin A (CgA, P = 0.01), serum alkaline phosphatase (P = 0.01), urinary N-telopeptide (NTX, P = 0.002) and lower hemoglobin values (P = 0.01), while hypercalcemic patients (n=16) had higher plasma CgA (P = 0.001) and serum lactate dehydrogenase values (P = 0.001), higher bone pain (P = 0.003) and a lower frequency of pure osteoblastic lesions (P = 0.001). Hypercalcemia was significantly associated with poor prognosis: hazard ratio (HR), 1.9 (95% confidence Interval (CI) 1.2-3.3) and higher risk to develop SREs HR, 2.5 (95% CI 1.2-5.2, P=0.01), while hypocalcemia was not associated with poor prognosis. The prognostic role of hypercalcemia was maintained in multivariate analysis after adjusting for validated prognostic parameters: HR, 2.72 (95% CI 1.1-6.8, P = 0.03). These data suggest that serum calcium levels should be taken into account in the clinical decision-making process of bone metastatic prostate cancer patients. Patients with asymptomatic hypercalcemia could benefit of a strict follow-up and an immediate bisphosphonate treatment. Further prospective clinical trials are needed to confirm this finding.

Twardowski, P. W., et al. (2013). "A phase II trial of dasatinib in patients with metastatic castration-resistant prostate cancer treated previously with chemotherapy." Anti-Cancer Drugs 24(7): 743-753.

There is a need for efficacious therapies for metastatic castration-resistant prostate cancer (mCRPC) after disease progression on docetaxel. The SRC tyrosine kinase and its related family members may be important drivers of prostate cancer and can be inhibited by dasatinib. mCRPC patients, after one previous chemotherapy, started dasatinib at 70 mg twice daily, amended to 100 mg daily. The primary endpoint was the disease control (DC) rate, defined as complete response (CR), partial response (PR), or stable disease (SD) in prostate specific antigen (PSA), RECIST, bone scan, and FACT-P score. Up to 41 patients were to be accrued (two-stage design, 21+20) to rule out a null-hypothesized effect of 5 versus 20% (=0.05, =0.1). Secondary endpoints included progression-free survival, toxicity, and pharmacokinetic and pharmacodynamic correlatives. Of 38 patients, 27 were evaluable for response or toxicity. The median duration of therapy was 55 days (6-284). Five patients showed DC after 8 weeks of therapy (18.5% DC, 95% CI: 6.3-38.1%). One PR (3.7% response rate, 95% CI: 0.1-19.0%) was observed in a patient treated for 284 days. Twelve patients (43%) discontinued treatment for toxicity. Dasatinib induced a decrease in phytohemagglutinin-stimulated CSF2, CD40L, GZMB, and IL-2 mRNAs in blood cells, indicating target engagement. Decreases in plasma IL-6 and bone alkaline phosphatase, and in urinary N-telopeptide, were associated with DC. Dasatinib has definite but limited activity in advanced mCRPC, and was poorly tolerated. The observation of a patient with prolonged, objective, clinically significant benefit warrants molecular profiling to select the appropriate patient population. (C) 2013 Wolters Kluwer Health vertical bar Lippincott Williams & Wilkins.

Ud Din, N., et al. (2011). "Utility of p63 immunohistochemical stain in differentiating urothelial carcinomas from adenocarcinomas of prostate." Indian journal of pathology & microbiology 54(1): 59-62.

BACKGROUND: Prostatic adenocarcinoma and urothelial carcinoma of the urinary bladder are common cancers in men. High grade forms of these tumors may present ambiguous morphologic features that do not permit a definite diagnosis. This distinction between the two tumors has significant staging and therapeutic implications. Hence, an accurate diagnosis is essential for optimal patient care. p63 is a new marker which can be used in this context. It is expressed in most of the urothelial carcinomas and negative in majority of prostatic adenocarcinomas. AIM: To compare the expression of p63 in urothelial carcinomas and adenocarcinomas of prostate. MATERIALS AND METHODS: Comparative cross--sectional study was carried out at a tertiary cancer hospital from 15 June 2006 to 15 December 2006. Immunohistochemical stain p63 was performed on 50 cases of urothelial carcinoma and 50 prostatic adenocarcinomas. Patients' name, age, histology numbers, grade of tumor, and expression of p63 were recorded. p63 expression was seen in 44 of 50 urothelial carcinomas (88%). None of the prostatic adenocarcinomas expressed p63. The ages of patients with prostatic adenocarcinoma ranged from 49 to 86 years with a median age of 71 years and 41 to 83 years for urothelial carcinomas with a median age of 60.5 years. CONCLUSION: p63 can be used as a reliable marker to distinguish prostatic adenocarcinomas from urothelial carcinomas in difficult cases in conjunction with other markers like PSA.

Ueckert, S., et al. (2013). "Phosphodiesterase type 5 (PDE5) is co-localized with key proteins of the nitric oxide/cyclic GMP signaling in the human prostate." World Journal of Urology 31(3): 609-614.

Experimental studies have provided the basis for the evaluation of inhibitors of the phosphodiesterase type 5 (PDE5) in the treatment of lower urinary tract symptomatology (LUTS) secondary to benign prostatic hyperplasia (BPH). It has been speculated that the clinical efficacy of PDE5 inhibitors in patients with LUTS/BPH can be explained by their effects on the urinary bladder rather than on the prostate. Hence, the significance of the nitric oxide (NO)/cyclic GMP signaling in the control of the human prostate requires further clarification. The present study aimed to investigate by means of immunohistochemistry in the human prostate the expression and distribution of key mediators of the NO pathway, namely cyclic GMP, the neuronal nitric oxide synthase (nNOS), and cyclic GMP-binding protein kinases type I (cGKI alpha, cGKI), in relation to PDE5, protein kinase A (cAK), and the vasoactive intestinal polypeptide (VIP). In the smooth muscle portion of the transition zone, immunosignals specific for the PDE5 were found co-localized with cyclic GMP, cGKI alpha, and cGKI, as well as with the cyclic cAMP-binding protein kinase A. Smooth muscle bundles were seen innervated by slender varicose nerves characterized by the expression of nNOS. Some of these nerves also presented staining related to the neuropeptide VIP. The findings give hints that the cyclic GMP- and cyclic AMP-dependent signal transduction may synergistically work together in regulating muscle tension in the transition zone. This might be of significance for the identification of new pharmacological avenues to treat patients with symptomatic BPH.

Usmani, N., et al. (2014). "Single-nucleotide polymorphisms studied for associations with urinary toxicity from I-125 prostate brachytherapy implants." Brachytherapy 13(3): 285-291.

PURPOSE: To identify clinical, dosimetric, and genetic factors that are associated with late urinary toxicity after a I-125 prostate brachytherapy implant. METHODS AND MATERIALS: Genomic DNA from 296 men treated with 125I prostate brachytherapy monotherapy was extracted from saliva samples for this study. A retrospective database was compiled including clinical, dosimetric, and toxicity data for this cohort of patients. Fourteen candidate single-nucleotide polymorphism (SNPs) from 13 genes (TP53, ERCC2, GSTP1, NOS, TGF beta 1, MSH6, RAD51, ATM, LIG4, XRCC1, XRCC3, GSTA1, and SOD2) were tested in this cohort for correlations with toxicity. RESULTS: This study identified 217 men with at least 2 years of followup. Of these, 39 patients developed Grade late urinary complications with a transurethral resection of prostate, urethral stricture, gross hematuria, or a sustained increase in their International Prostate Symptom Score. The only clinical or dosimetric factor that was associated with late urinary toxicity was age (p = 0.02). None of the 14 SNPs tested in this study were associated with late urinary toxicity in the univariate analysis. CONCLUSIONS: This study identified age as the only variable being associated with late urinary toxicity. However, the small sample size and the candidate gene approach used in this study mean that further investigations are essential. Genome-wide association studies are emerging as the preferred approach for future radiogenomic studies to overcome the limitations from a candidate gene approach. Crown Copyright (c) 2014 Published by Elsevier Inc. on behalf of American Brachytherapy Society. All rights reserved.

Valdevenito Sepulveda, J. P. and E. Hernandez (2007). "Discontinued oral ciprofloxacin for transurethral resection of the prostate in patients with sterile urine without preoperative bladder catheter." Archivos espanoles de urologia 60(10): 1.189-181.196.

OBJECTIVES: To describe the rate of infectious complications using discontinuous oral ciprofloxacin in transurethral resection of the prostate. To weigh up the influence of clinical background, surgical complications and postoperative outcome on the development of such complications. To compare the results to those obtained will equal methodology using antibiotics until catheter removal. METHODS: A prospective open study was designed including 105 consecutive patients with sterile urine and without indwelling catheter subjected to transurethral resection of the prostate. Patients received oral ciprofloxacin 500 mg (4 doses) on call to the surgical room, the night of the surgery, next morning of surgery and before catheter removal. RESULTS: One hundred patients are analyzed. Fever was present in 10% patients (axillary temperature equal or over 37.5 degrees C). Systemic clinical infection was present in 3% patients (axillary temperature over 38 degrees C and C-reactive protein over 40 mg/l). No isolated postoperative bacteriuria was present (colony count > 10(5) CFU/ ml). Active chronic prostatitis was statistically asociated to fever (p= 0,018) and to systemic clinical infection (p= 0,016). Previous urinary tract infection antecedent was statistically associated to active chronic prostatitis on histopathology (p= 0,049). CONCLUSIONS: This study shows some clinical evidence supporting that previous urinary tract infection antecedent is a risk factor of infectious complications after transurethral resection of the prostate and that prostate bearing microorganisms may be responsible for some of them in this kind of patients. An antibiotic dose before catheter removal seem to reduce postoperative bacteriuria.

Valmu, L., et al. (2010). "Proteomic analysis of pancreatic secretory trypsin inhibitor/tumor-associated trypsin inhibitor from urine of patients with pancreatitis or prostate cancer." Methods in molecular biology (Clifton, N.J.) 641: 347-357.

The development of proteomic methods, especially mass spectrometry, has brought new possibilities to tumor marker research. Pancreatic secretory trypsin inhibitor (PSTI), a common known biomarker for various malignancies, occurs on genetic variants that we are able to detect at the protein level with proteomic techniques using immunoaffinity capture prior to liquid chromatography-mass spectrometry (LC-MS). We also show that PSTI can be detected in urine from cancer patients using a two-step peptide enrichment technique and LC-MS. These results show that tumor-associated peptides can be detected in urine by proteomic techniques.

van Oorschot, B., et al. (2014). "Reduced Activity of Double-Strand Break Repair Genes in Prostate Cancer Patients With Late Normal Tissue Radiation Toxicity." International Journal of Radiation Oncology Biology Physics 88(3): 664-670.

Purpose: To investigate clinical parameters and DNA damage response as possible risk factors for radiation toxicity in the setting of prostate cancer. Methods and Materials: Clinical parameters of 61 prostate cancer patients, 34 with (overresponding, OR) and 27 without (non-responding, NR) severe late radiation toxicity were assembled. In addition, for a matched subset the DNA damage repair kinetics (gamma-H2AX assay) and expression profiles of DNA repair genes were determined in ex vivo irradiated lymphocytes. Results: Examination of clinical data indicated none of the considered clinical parameters to be correlated with the susceptibility of patients to develop late radiation toxicity. Although frequencies of gamma-H2AX foci induced immediately after irradiation were similar (P = .32), significantly higher numbers of gamma-H2AX foci were found 24 hours after irradiation in OR compared with NR patients (P = .03). Patient-specific gamma-H2AX foci decay ratios were significantly higher in NR patients than in OR patients (P < .0001). Consequently, NR patients seem to repair DNA double-strand breaks (DSBs) more efficiently than OR patients. Moreover, gene expression analysis indicated several genes of the homologous recombination pathway to be stronger induced in NR compared with OR patients (P < .05). A similar trend was observed in genes of the nonhomologous end-joining repair pathway (P = .09). This is congruent with more proficient repair of DNA DSBs in patients without late radiation toxicity. Conclusions: Both gene expression profiling and DNA DSB repair kinetics data imply that less-efficient repair of radiation-induced DSBs may contribute to the development of late normal tissue damage. Induction levels of DSB repair genes (eg, RAD51) may potentially be used to assess the risk for late radiation toxicity. (C) 2014 Elsevier Inc.

Varambally, S., et al. (2008). "Golgi Protein GOLM1 Is a Tissue and Urine Biomarker of Prostate Cancer." Neoplasia 10(11): 1285-U1104.

Prostate cancer is the most common type of tumor found in American men and is the second leading cause of cancer death in males. To identify biomarkers that distinguish prostate cancer from normal, we compared multiple gene expression profiling studies. Through meta-analysis of expression array data from multiple prostate cancer studies, we identified GOLM1 (Golgi membrane protein 1, Golm 1) as consistently up-regulated in clinically localized prostate cancer. This observation was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) and validated at the protein level by immunoblot assay and immunohistochemistry. Prostate epithelial cells were identified as the cellular source of GOLM1 expression using laser capture microdissection. Immunohistochemical staining localized the GOLM1 signal to the subapical cytoplasmic region, typical of a Golgi distribution. Surprisingly

Varinot, J., et al. (2013). "HOXB13 is a sensitive and specific marker of prostate cells, useful in distinguishing between carcinomas of prostatic and urothelial origin." Virchows Archiv 463(6): 803-809.

The origin of a primary or metastatic carcinoma in the pelvic area is sometimes difficult to establish, in particular the distinction between those originating in the bladder and the prostate. A candidate marker is the HOXB13 gene, essential for prostate development. Some studies have shown expression of HOXB13 protein by immunohistochemistry in the nuclear compartment of benign prostate luminal epithelium and prostate carcinoma. Forty-two cases of biopsies and resection specimens of the prostate and urinary bladder, metastatic lymph nodes, and pelvic masses were retrieved from our databases. In all cases, doubt persisted regarding prostatic versus urothelial origin. All cases were stained for CK7, p63, p504s, PSA, CK20, and HOXB13. Chromogranin A, CD56, and synaptophysin were used when neuroendocrine differentiation was suspected. HOXB13 staining was negative or only weakly positive in all carcinomas of urothelial origin. Three of four carcinomas with neuroendocrine differentiation did not express HOXB13. The fourth carcinoma, in a patient with a history of prostate carcinoma, was positive. In two cases with a synchronous prostatic and urothelial carcinoma, HOXB13 was exclusively expressed in the prostatic carcinoma. Our results demonstrate that HOXB13 expression identifies prostatic origin of a carcinoma with good sensitivity (89 %) and very good specificity (100 %). HOXB13 is a specific and sensitive marker for prostate cells and a valuable diagnostic tool, especially when poorly differentiated or neuroendocrine tumors are encountered. These results justify testing of HOXB13 as a prostate-specific carcinoma marker in larger cohorts for a more thorough evaluation of its sensitivity and specificity.

Vermassen, T., et al. (2012). "Glycosylation of prostate specific antigen and its potential diagnostic applications." Clinica Chimica Acta 413(19-20): 1500-1505.

Prostate specific antigen (PSA) assays are widely used for early detection of prostate cancer. However, those analyses are associated with considerable sensitivity and specificity problems. Several approaches have been developed to tackle this issue. PSA is a glycoprotein, which is primarily produced by the prostatic epithelial cells. Aberrant glycosylation modification of proteins is a fundamental characteristic of tumorigenesis. Study of PSA glycoforms offers interesting diagnostic perspectives. Modern technology allows us to analyze PSA glycoforms in a variety of clinical samples (serum or plasma, urine, seminal fluid, tissue). A number of novel techniques, such as lectin-based detection methods, mass spectrometry, 2-dimensional electrophoresis and capillary electrophoresis have been developed to analyze PSA glycosylation. This article reviews the technical and diagnostic aspects of PSA glycoforms. (C) 2012 Elsevier B.V. All rights reserved.

Vermassen, T., et al. (2015). "Urinary Prostate Protein Glycosylation Profiling as a Diagnostic Biomarker for Prostate Cancer." Prostate 75(3): 314-322.

BACKGROUND. Serum prostate-specific antigen (sPSA) measurement is widely used as opportunistic screening tool for prostate cancer (PCa). sPSA suffers from considerable sensitivity and specificity problems, particularly in the diagnostic gray zone (sPSA 4-10 mu g/L). Furthermore, sPSA is not able to discriminate between poorly-, moderately-, and well-differentiated PCa. We investigated prostatic protein glycosylation profiles as a potential PCa biomarker. METHODS. Differences in total urine N-glycosylation profile of prostatic proteins were determined between healthy volunteers (n = 54), patients with benign prostate hyperplasia (BPH; n = 93) and newly diagnosed PCa patients (n = 74). Variations in N-glycosylation profile and prostate volume were combined into one urinary glycoprofile marker (UGM). Additionally, differences in N-glycosylation were identified between Gleason <7, = 7, and >7. RESULTS. The UGM was able to discriminate BPH from PCa, overall and in the diagnostic gray zone (P < 0.001). The UGM showed comparable diagnostic accuracy to sPSA, but gave an additive diagnostic value to sPSA (P < 0.001). In the diagnostic gray zone the UGM performed significantly better than sPSA (P < 0.001). A significant difference was found in core-fucosylation of biantennary structures and overall core-fucosylation of multiantennary structures between Gleason < 7 and Gleason > 7 (P = 0.010 and P = 0.020, respectively) and between Gleason = 7 and Gleason >7 (P = 0.011 and P = 0.025, respectively). CONCLUSIONS. The UGM shows high potential as PCa biomarker, particularly in the diagnostic gray zone. Further research is needed to validate these findings. (C) 2014 Wiley Periodicals, Inc.

Vermassen, T., et al. (2014). "Capillary electrophoresis of urinary prostate glycoproteins assists in the diagnosis of prostate cancer." Electrophoresis 35(7): 1017-1024.
Prostate marker assays are widely used for detection of prostate cancer (PCa) but are associated with considerable sensitivity and specificity problems. Therefore, we investigated prostatic protein glycosylation profiles as a potential biomarker. We determined the urinary asparagine-linked glycan (N-glycan) profile of prostatic proteins of healthy volunteers (n = 25), patients with benign prostate hyperplasia (BPH; n = 62) and newly diagnosed PCa patients (n = 42) using DNA-sequencer-assisted fluorophore-assisted carbohydrate electrophoresis. Through squeezing of the prostate, a sufficient amount of prostatic proteins was obtained for direct structural analyses of N-glycan structures. N-glycans of PCa compared to BPH were characterized by a significant decrease in triantennary structures (p = 0.047) and overall fucosylation (p = 0.026). Prostate-specific antigen (PSA) and the urinary glycoprofile marker showed comparable overall receiver operating characteristic curve analysis as well as in the diagnostic gray zone with serum PSA values between 4 and 10g/L. However, when combining PSA and the urinary glycoprofile marker, the latter gave an additive diagnostic value to serum PSA (p 0.001). In conclusion, N-glycosylation profiling demonstrated differences between BPH and PCa. These changes could lead to the discovery of a new biomarker for PCa.

Vestergaard, M. d. and E. Tamiya (2007). "A rapid sample pretreatment protocol: Improved sensitivity in the detection of a low-abundant serum biomarker for prostate cancer." Analytical Sciences 23(12): 1443-1446.
We have developed a rapid immunoglobulin G (IgG) and a human serum albumin (HSA) depletion protocol. We depleted both HSA and IgG (> 97%) separately, and in a single procedure. The method is specific and reproducible (RSD < 1.0%), and substantially lowered the detection limit of prostate-specific antigen, a prostate cancer biomarker. The method can be applied to other biomarkers and proteomic studies. Interestingly, the depletion of HSA might not be blankly as beneficial as widely portrayed. Our study suggests the depletion of IgG to be more beneficial than albumin depletion.

Voeghtly, L. M., et al. (2009). "Potential Clinical Importance of the Activation Peptide of Prostate-specific Antigen." International Journal of Clinical and Experimental Pathology 2(6): 588-598.

Prostate cancer is the second leading cause of cancer death in men. Prostate specific antigen (PSA) is currently the best marker available for screening and monitoring disease recurrence, but its use has limitations. This study investigates the biosynthesis, secretion and activation of PSA in a prostate adenocarcinoma cell line. PSA is secreted as a pro-enzyme containing a seven amino acid activation peptide (APLILSR). Because the activation peptide is removed extracellularly in vivo, we hypothesized that it may be detected in the blood or urine. Activated PSA is a serine protease and reacts rapidly with protease inhibitors in the blood. These protein complexes are removed from the circulatory system by hepatocyte-mediated endocytosis. This rapid clearance likely interferes with detection of PSA in the early stages of prostate cancer. Notably these clearance mechanisms are not considered when PSA levels are determined clinically. We used radio-labeled proteins to determine the clearance of PSA in complex with its inhibitors as well as in vivo clearance of APLILSR. Dot blotting was used to determine the presence of APLILSR in human urine samples. Our data indicates that PSA-alpha 1-antichymotrypsin only accumulates in the blood when large amounts of PSA are present and saturate clearance mechanisms. We found that APLILSR is filtered from the bloodstream by the kidney, and is detectable in the urine of patients with prostate cancer, but not controls. We propose that urine detection of the PSA activation peptide may represent a clinically sensitive measure of PSA production/secretion.

Voelkel-Johnson, C. (2011). "TRAIL-mediated signaling in prostate, bladder and renal cancer." Nature Reviews Urology 8(8): 417-427.
Tumor necrosis factor related apoptosis inducing ligand (TRAIL) is a death receptor ligand that has the ability to preferentially initiate apoptosis in malignant cells with minimal toxicity to normal cells. TRAIL-based therapeutics, including recombinant TRAIL, TRAIL-receptor agonistic antibodies and TRAIL gene therapy, have now entered clinical trials. Although these therapeutics are promising, concerns regarding TRAIL resistance are causing research efforts to shift towards the identification of effective combination therapies. Small-molecule inhibitors, natural compounds, and drugs approved for treatment of diseases other than cancer have been shown to affect TRAIL receptors, antiapoptotic proteins and survival pathways in prostate, bladder and renal cell lines and in preclinical models. Changes in endogenous TRAIL and TRAIL receptor expression during the development of genitourinary malignancies and the way in which the expression pattern is affected by treatment are of great interest, and understanding the biological consequences of such changes will be important to maximize the potential of TRAIL-based therapeutics.

Waldkirch, E., et al. (2010). "Expression of cAMP-dependent Protein Kinase Isoforms in the Human Prostate: Functional Significance and Relation to PDE4." Urology 76(2).
OBJECTIVES To investigate the expression of isoforms of the cyclic AMP (cAMP)-dependent protein kinase (cAK) in the transition zone of the human prostate and the functional significance of the enzyme in the control of prostate smooth muscle. METHODS Using Western blot analysis and immunohistochemistry, the expression and distribution in the prostate of cAKI alpha, cAKI beta, cAKII alpha, and cAKII beta in relation to alpha-actin and the phosphodiesterase PDE4 (types A and B) were investigated. The effects of the cAK inhibitor Rp-8-CPT-cAMPS on the reversion of the adrenergic tension of isolated prostate tissue induced by forskolin, rolipram, sodium nitroprusside (SNP), and tadalafil were examined by means of the organ bath technique. RESULTS Immunosignals specific for cAKI alpha, cAKII alpha, and cAKII beta were observed in the smooth musculature and glandular structures of the prostate. Double stainings revealed the colocalization of alpha-actin and PDE4 with the cAK isoforms. The expression of the cAK isoforms was confirmed by Western blot analysis. The relaxation of the tension induced by norepinephrine brought about by forskolin, rolipram, SNP, and tadalafil was significantly attenuated by Rp-8-CPT-cAMPS. CONCLUSIONS The colocalization of smooth muscle alpha-actin and PDE4 with cAK, as well as the results from the organ bath experiments, provide further evidence for a pivotal role of the cAMP-dependent signaling in the regulation of prostate smooth muscle contractility. Compounds interacting with the cAMP/cAK pathway might represent a new therapeutic avenue to treat symptoms of benign prostatic hyperplasia and lower urinary tract symptomatology. UROLOGY 76: 515.e8-515.e14, 2010. (C) 2010 Elsevier Inc.

Waldkirch, E. S., et al. (2007). "Immunohistochemical distribution of cyclic GMP-dependent protein kinase-1 in human prostate tissue." European Urology 52(2): 495-502.

Objectives: Phosphodiesterase 5 (PDE5) inhibitors improve smooth muscle relaxation and therefore are considered for pharmacotherapy of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). Cyclic guanosine monophosphate (cGMP) -dependent protein kinase-1 (cGKI) has been identified as one of the downstream targets for cGMP. The aim of the present study was to evaluate, by means of immunohistochemistry and Western blot analysis, the expression and localization of cGKI isoforms in relation to smooth muscle alpha-actin and cGMP in the human prostate. Methods: Cryostat sections of tissue segments excised from the transition zone of human prostates from 11 patients (aged 54-68 yr) were incubated with primary antibodies directed against smooth muscle alpha-actin, cGMP, cGKI, c:GKI alpha, and cGKI beta. Visualization of double-labelled immunofluorescent staining was achieved by laser microscopy. Western blot analysis was performed to confirm the expression of cGKI isoforms. Results: Immunoreactivities specific for cGKI, cGKI alpha, and cGKI beta were observed in the smooth musculature of the transition zone. Double-staining revealed the colocalization of smooth muscle alpha-actin, cGMP, and cGKI isoforms in smooth muscle cells of the fibromuscular stroma. The expression of cGKI isoforms was confirmed by Western blot analysis. Conclusions: Our results confirm the presence of cGKI isoforms a and P in the transition zone of human prostate tissue. in addition, the colocalization of alpha-actin, cGMP, and cGKI isoforms provides further evidence for a significant role of the nitric oxide/cGMP pathway in the regulation of smooth muscle contractility in human prostate tissue and therefore could provide additional targets for pharmacotherapy of BPH and LUTS. (C) 2007 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Wallerand, H., et al. (2010). "Tyrosine-kinase inhibitors in the treatment of muscle invasive bladder cancer and hormone refractory prostate cancer." Archivos espanoles de urologia 63(9): 773-787.

OBJECTIVES: Various protein kinases are known to be activated in cancer cells and drive tumor growth and progression. In metastatic renal cell carcinoma tyrosine-kinase inhibitors (TKIs) have achieved significant progression-free and overall survival improvements. For bladder and prostate cancers TKIs may also be considered as a promising treatment option. Our aim was to report the most relevant published articles to support the interest of the use of TKIs in the treatment of bladder and prostate cancer. METHOD: PubMed database and bibliographies of retrieved articles were reviewed. The key words used were tyrosine-kinase inhibitor, protein-kinase inhibitor, hormone refractory prostate cancer, muscle invasive bladder cancer. The most relevant publications from basic science and clinical randomized controlled studies were summarized and analyzed. RESULTS: Regarding bladder cancer, TKI treatment is one of the most studied therapeutic strategies in the field of targeted therapy. Indeed, it has been suggested that targeting TK alone and/or in association with cytotoxic chemotherapy may represent a promising option for treating locally advanced and/or metastatic bladder cancer. Concerning hormone refractory prostate cancer (HRPC), collected data are still confusing. Basic science studies found an interesting expression of EGF and VEGF receptors on cancer cells supporting the idea that TKIs could be efficient in HRPC. Nonetheless most of published clinical phase II studies found a weak effect on symptoms and quality of life without any decrease in PSA levels or overall survival. CONCLUSION: TKIs have not yet achieved in bladder and prostate cancers similar efficacy to what has been obtained in metastatic renal cell carcinoma. Further studies are needed to establish the place of such an approach in non renal tumors.

Wallerand, H., et al. (2010). "The epithelial-mesenchymal transition-inducing factor TWIST is an attractive target in advanced and/or metastatic bladder and prostate cancers." Urologic Oncology-Seminars and Original Investigations 28(5): 473-479.

Purpose: Metastasis remains the main cause of death in both bladder (BCa) and prostate (PCa) cancers. The results of chemotherapy did not show any significant improvement of the survival the past years. Cancer research has led to the identification of signaling pathways involved and molecular targets that could change the natural history. The epithelial-mesenchymal transition (EMT), critical during embryonic development, becomes potentially destructive in many epithelial tumors progression where it is inappropriately activated. The cell-cell and cell-extracellular matrix interactions are altered to release cancer cells, which are able to migrate toward metastatic sites. Hallmarks of EMT include the down-regulation of E-cadherin expression, which is the main component of the adherens junctions. The protein TWIST is a transcriptional repressor of E-cadherin, tumor progression, and metastasis, and could be used as a molecular target to restore the chemosensitivity in BCa and PCa. Materials and methods: We selected the last 5-year basic research literature on EMT and TWIST but also clinical studies on BCa and PCa in which TWIST is overexpressed and could be considered as an efficient prognostic marker and molecular target. Results: TWIST is considered as a potential oncogene promoting the proliferation and inhibiting the apoptosis. TWIST promotes the synthesis of the pro-angiogenic factor, vascular endothelial growth factor (VEGF) involved in tumor progression and metastasis. Apoptosis and angiogenesis are two essential cancer progression steps in many epithelial tumors, including BCa and PCa. Conclusions: With the targeted therapy, oncology has entered into a new era, which is going to be critical in cancer treatment in combination with traditional anticancer drugs. (C) 2010 Elsevier Inc. All rights reserved.

Walther, S., et al. (2012). "Expression and Alpha1-adrenoceptor Regulation of Caldesmon in Human Prostate Smooth Muscle." Urology 79(3).

OBJECTIVE To investigate expression and alpha 1-adrenergic regulation of caldesmon in the human prostate. Caldesmon is an important mediator and regulator of contraction in different smooth muscle types. However, this has not been investigated in the prostate to date. The activity of caldesmon may be tightly regulated by serine-789 phosphorylation. MATERIALS AND METHODS Prostate tissue was obtained from patients undergoing radical prostatectomy. Caldesmon expression was studied by Western blot analysis and immunohistochemistry. The adrenergic regulation of caldesmon phosphorylation was investigated by Western blot analyses with a site-and phosphospecific antibody. RESULTS Caldesmon expression was detectable by Western blot analysis in all investigated samples of human prostates (n = 8 patients). Immunoreactivity after staining with a caldesmon antibody was strong in smooth muscle cells, but not observed in glandular or epithelial cells (n = 5 patients). In double fluorescence staining, caldesmon co-localized with alpha 1A-adrenoceptors and alpha-smooth muscle actin (n = 6 patients). Stimulation of prostate tissue with noradrenaline (30 mu M, n = 6 patients) or the alpha 1-adrenergic agonist phenylephrine (10 mu M, n = 6 patients) resulted in progressive phosphorylation of caldesmon at serine-789. Noradrenaline-induced caldesmon phosphorylation was 1.5 +/- 0.2-fold after 5 minutes (P<.04 vs basal phosphorylation), and 1.6 +/- 0.2-fold after 10 minutes (P<.04). Phenylephrine-induced caldesmon phosphorylation was 1.7 +/- 0.2-fold after 10 minutes (P<.02 vs basal phosphorylation), and 2.4 +/- 0.6-fold after 20 minutes (P<.05). CONCLUSIONS Caldesmon is an effector of alpha 1-adrenoceptors in the human prostate. Caldesmon activation may be of importance for alpha 1-adrenergic prostate contraction, and during therapy with alpha 1-blockers. UROLOGY 79: 745.e5-745.e12, 2012. (C) 2012 Published by Elsevier Inc.

Wang, C., et al. (2011). "Adult prostate sarcoma: a clinicopathologic study of 15 cases." Zhonghua bing li xue za zhi Chinese journal of pathology 40(11): 749-753.

OBJECTIVE: To clarify the clinical and morphological features of adult prostate sarcoma (APS) and to further improve the knowledge and diagnostic accuracy for APS. METHODS: Fifteen cases of APS were observed and analyzed on the clinical symptom, pathological features, treatment and prognosis. RESULTS: Age of onset ranged from 22 to 77 years (mean 46.3 years). The majority of cases were presented with dysuresia. By digital rectal examination and imaging of the prostate, APS was often identified as a large tumor mass. There were 6 cases of leiomyosarcomas, 6 embryonal rhabdomyosarcomas, and 3 fibrosarcomas in this series. Follow-up data were available for 12 cases: 7 cases died of the disease between 9 days and 360 days after surgery. Among 5 survived patients, 3 cases had recurrence after 2 to 24 months follow-up. CONCLUSIONS: APS is a rare tumor that typically has clinical features: earlier age of onset, fast-appeared urinary tract symptoms, significant mass effects, and poor outcome. Level of prostate specific antigen (PSA) is usually normal or lower. Final diagnosis relies on the features of histology and immunohistochemistry expression profile.

Wang, D., et al. (2010). "Prostate stem cell antigen enhancer and uroplakin II promoter based bladder cancer targeted tissue-specific vector." Urologic Oncology-Seminars and Original Investigations 28(2): 164-169.

Purpose: To construct a dual specific vector which contains prostate stem cell antigen enhancer (PSCAE) and uroplakin II (UPII) promoter targeted bladder cancer. Methods: UPII promoter and PSCAE were amplified by polymerase chain reaction (PCR). Luciferase gene (LUC) was obtained from plasmid pBK-CMV-LUC. PSCAE. UPII promoter and LUC were inserted into shuttle plasmid to create Rp-UPII-LUC and Rp-PSCAE-UPII-LUC. Rp-UPII-LUC and Rp-PSCAE-UPII-LUC were cotransfected with pCMV-beta-gal into various cell lines at the presence or absence of androgen receptor agonist R1881 and androgen receptor antagonist flutamide. Luminescence was detected with luciferase assay kit and counted on liquid scintillation counter. Results: Bladder cancer cells showed higher LUC activity than non-bladder cancer cells after transfected with plasmids Rp-UPII-LUC and Rp-PSCAE-UPII-LUC. PSCAE could improve the LUC activity in both AR positive and AR negative bladder cancer cells but not in non-bladder cancer cells and normal human urothelial (NHU) cells. R1881 could increase the LUC activity in AR positive bladder cancer cells but not in AR negative bladder cancer cells and non-bladder cancer cells. Flutamide could not inactivate PSCAE in bladder cancer cells. Conclusions: PSCAE can improve target gene expression in bladder cancer cells but not in non-bladder cancer cells and NHU cells. PSCAE maintains a certain level of androgen independent activity in bladder cancer cells. PSCAE is active in both AR positive and AR negative bladder cancer cells. The results suggest that combination of PSCAE with UPII promoter is feasible in constructing bladder cancer-specific vectors. (C) 2010 Elsevier Inc. All rights reserved.

Wang, T.-C., et al. (2012). "Effects of Chronic Chromate Exposure on Human Serum Prostate Specific Antigen: A Cross Sectional Study." Industrial Health 50(2): 95-102.

The detrimental effect of chronic chromium (Cr) exposure on the prostate has never been studied. Here, we report the prostate specific antigen (PSA) changes in occupational chromate exposed workers. In this study, eighty six male occupational chromate exposed workers and forty five age-matched controls were recruited. The concentration of Cr in urine (U-Cr), serum total PSA (tPSA), free PSA (fPSA), high sensitive C reactive protein (Hs-CRP) and peripheral white blood cells count (WBC) were measured. The results show that the U-Cr, serum tPSA, Hs-CRP and WBC were significantly higher in Cr exposed workers when compared to the controls. Contrastively, the serum fPSA level in Cr exposed workers was lower than controls. A significant positive correlation between U-Cr and serum tPSA was observed. Multiple linear regression analysis revealed that serum tPSA and fPSA level was statistically associated with the serum Hs-CRP and U-Cr concentration in Cr exposed workers. These observations suggested that chronic Cr exposure could produce potential prostate injury and the nonspecific inflammation at least might be one of the reasons to explain the elevated concentration of tPSA in chronic occupational chromate exposed workers.

Warrick, J. I., et al. (2014). "Evaluation of tissue PCA3 expression in prostate cancer by RNA in situ hybridization- a correlative study with urine PCA3 and TMPRSS2-ERG." Modern Pathology 27(4): 609-620.

PCA3 is a prostate-specific non-coding RNA, with utility as a urine-based early detection biomarker. Here, we report the evaluation of tissue PCA3 expression by RNA in situ hybridization in a cohort of 41 mapped prostatectomy specimens. We compared tissue PCA3 expression with tissue level ERG expression and matched pre-prostatectomy urine PCA3 and TMPRSS2-ERG levels. Across 136 slides containing 138 foci of prostate cancer, PCA3 was expressed in 55% of cancer foci and 71% of high-grade prostatic intraepithelial neoplasia foci. Overall, the specificity of tissue PCA3 was >90% for prostate cancer and high-grade prostatic intraepithelial neoplasia combined. Tissue PCA3 cancer expression was not significantly associated with urine PCA3 expression. PCA3 and ERG positivity in cancer foci was positively associated (P<0.01). We report the first comprehensive assessment of PCA3 expression in prostatectomy specimens, and find limited correlation between tissue PCA3 and matched urine in prostate cancer.

Wayner, E. A., et al. (2012). "Development of an ELISA to detect the secreted prostate cancer biomarker AGR2 in voided urine." Prostate 72(9): 1023-1034.

BACKGROUND Comparative transcriptomics between sorted cells identified AGR2 as one of the highest up-regulated genes in cancer. Overexpression in primary tumors was verified by tissue microarray analysis. AGR2 encodes a 19-kDa secreted protein that might be found in urine. METHODS Monoclonal antibodies were generated against AGR2. One antibody pair, P1G4 (IgG1) to capture and P3A5 (IgG2a) to detect, showed good performance characteristics in a sandwich ELISA. This assay could detect AGR2 at sub ng/ml quantities. RESULTS AGR2 was detected in tissue digestion media of tumor specimens and culture media of AGR2-secreting prostate cancer cell lines. Additional testings involved frozen section immunohistochemistry, immunoprecipitation, and Western blot analysis. Voided urine samples were collected from pre-operative cancer patients, and urinary protein was desalted and concentrated by filtration. The amount of AGR2 detected was scored as pg/100?mu g total protein, and then converted to pg/ml urine. The developed ELISA detected AGR2 protein, ranging from 3.6 to 181?pg/ml, in an initial cohort of samples. AGR2 was not detected in the urine of non-cancer and a bladder cancer patient. CONCLUSIONS For prostate cancer, an AGR2 urine test could be used for diagnosis. The data, although derived from a small number of samples assayed, showed that developing such a test for clinical application is viable because AGR2 is specific to cancer cells, and apparently secreted into urine. Prostate 72:10231034, 2012. (c) 2011 Wiley Periodicals, Inc.

Weber, A., et al. (2008). "The FUSE binding proteins FBP1 and FBP3 are potential c-myc regulators in renal, but not in prostate and bladder cancer." Bmc Cancer 8.

Background: The three far-upstream element (FUSE) binding proteins (FBP1, FBP2, and FBP3) belong to an ancient family of single-stranded DNA binding proteins which are required for proper regulation of the c-myc proto-oncogene. Whereas it is known that c-myc alterations play a completely different role in various carcinomas of the urogenital tract, the relevance of FBPs is unclear. Methods: FBP1, FBP3 and c-myc expression was studied in 105 renal cell, 95 prostate and 112 urinary bladder carcinomas by immunohistochemistry using tissue microarrays. Results: High rates of FBP1 and FBP3 expression were observed in all cancer types. There was a concomitant up-regulation of FBP1 and FBP3 in renal cell and prostate carcinomas (p < 0.001 both). C-myc expression was detectable in 21% of prostate, 30% of renal and 34% of urothelial carcinomas. Interestingly, strong FBP1 and FBP3 expression was associated with c-myc up-regulation in clear cell renal cell carcinomas (p < 0.001 and 0.09 resp.), but not in bladder or prostate cancer. Conclusion: The correlation between FBP1/FBP3, c-myc and high proliferation rate in renal cell carcinoma provides strong in vivo support for the suggested role of FBP1 and FBP3 as activators of c-myc. The frequent up-regulation of FBP1 and FBP3 in urothelial and prostate carcinoma suggests that FBPs also have an important function in gene regulation of these tumors.

Whelan, C., et al. (2013). "The influence of PSA-RNA yield on the analysis of expressed prostatic secretions (EPS) for prostate cancer diagnosis." Canadian Journal of Urology 20(1): 6597-6602.

WHELAN C, CROCITTOL L, KAWACHIM, CHAN K, SMITH D, WILSON T, SMITH S. The influence of PSA-RNA yield on the analysis of expressed prostatic secretions (EPS) for prostate cancer diagnosis. Can J Urol 2013;20(1):6597-6602. Introduction: In patients with prostate cancer, luminal prostate-specific antigen (P SA) enters the circulation because the basement membrane and glandular epithelium are damaged. Given that excess mobilization of prostate cells during prostatic massage can influence normalization in diagnostic testing, we studied P S A mRNA levels in expressed prostatic secretions (EPS) from patients undergoing biopsy for prostate cancer to determine if prostate cells are preferentially mobilized from patients with prostate cancer during prostatic massage. Materials and methods: Quantitative Reverse-Transcription PCR (qRT-PCR) was used to measure the RNA levels of GAPDH, PSA, TMPRSS2:ERG and PCA3 in EPS specimens obtained from patients undergoing biopsy for prostate cancer. Results: The level of PSA mRNA is significantly elevated in EPS specimens obtained from patients with a subsequent diagnosis of prostate cancer. This correlation influenced diagnostic testing results from EPS in two ways. First, when used as an exclusion parameter it appears to improve the diagnostic performance of TMPRSS2:ERG in EPS. Second, when used as a normalization parameter it appears to decrease the performance of these same tests. Conclusion: When comparing the results of mRNA based prostate cancer diagnostics in EPS it will be essential to consider PSA mRNA as a prostate specific gene and not a housekeeping gene.

Whitaker, H. C., et al. (2010). "The rs10993994 Risk Allele for Prostate Cancer Results in Clinically Relevant Changes in Microseminoprotein-Beta Expression in Tissue and Urine." PloS one 5(10).

Background: Microseminoprotein-beta (MSMB) regulates apoptosis and using genome-wide association studies the rs10993994 single nucleotide polymorphism in the MSMB promoter has been linked to an increased risk of developing prostate cancer. The promoter location of the risk allele, and its ability to reduce promoter activity, suggested that the rs10993994 risk allele could result in lowered MSMB in benign tissue leading to increased prostate cancer risk. Methodology/Principal Findings: MSMB expression in benign and malignant prostate tissue was examined using immunohistochemistry and compared with the rs10993994 genotype. Urinary MSMB concentrations were determined by ELISA and correlated with urinary PSA, the presence or absence of cancer, rs10993994 genotype and age of onset. MSMB levels in prostate tissue and urine were greatly reduced with tumourigenesis. Urinary MSMB was better than urinary PSA at differentiating men with prostate cancer at all Gleason grades. The high risk allele was associated with heterogeneity of MSMB staining and loss of MSMB in both tissue and urine in benign prostate. Conclusions: These data show that some high risk alleles discovered using genome-wide association studies produce phenotypic effects with potential clinical utility. We provide the first link between a low penetrance polymorphism for prostate cancer and a potential test in human tissue and bodily fluids. There is potential to develop tissue and urinary MSMB for a biomarker of prostate cancer risk, diagnosis and disease monitoring.

Wittke, S., et al. (2007). "Capillary electrophoresis coupled to mass spectrometry for proteome analysis. An innovative diagnostic method for prostate and bladder cancer." Urologe 46(7): 733-739.

We developed a proteomics-based technology for the non-invasive detection of urothelial and prostate carcinoma. Using capillary electrophoresis coupled to mass spectrometry, disease-specific changes in the urinary proteome were detected and subsequently relevant polypeptides were employed as disease-specific biomarkers. Here we report the results of various studies including approximately 1,000 patients with different diseases and healthy volunteers. The results of these studies revealed that prostate and urothelial carcinoma can be detected by using disease-specific polypeptide patterns. Preliminary results also indicate that the tumour stage of an urothelial carcinoma can be estimated by this approach. In conclusion, this new and non-invasive application might help to improve the diagnostic methods already available.

Wood, S. L., et al. (2013). "Proteomic studies of urinary biomarkers for prostate, bladder and kidney cancers." Nature Reviews Urology 10(4): 206-218.

Urine is an ideal body fluid for the detection of protein markers produced by urological cancers as it can be sampled noninvasively and contains secreted and directly shed proteins from the prostate, bladder and kidney. Major challenges of working with urine include high inter-individual and intra-individual variability, low protein concentration, the presence of salts and the dynamic range of protein expression. Despite these challenges, significant progress is being made using modern proteomic methods to identify and characterize protein-based markers for urological cancers. The development of robust, easy-to-use clinical tests based on novel biomarkers has the potential to impact upon diagnosis, prognosis and monitoring and could revolutionize the treatment and management of these cancers.

Wright, J. L. and P. H. Lange (2007). "Newer potential biomarkers in prostate cancer." Reviews in urology 9(4): 207-213.

Prostate-specific antigen (PSA) screening has led to a significant rise in the number of men diagnosed with prostate cancer and an associated increase in biopsies performed. Despite its limitations, including a positive predictive value of only 25%-40%, PSA remains the only generally accepted biomarker for prostate cancer. There is a need for better tools to not only identify men with prostate cancer, but also to recognize those with potentially lethal disease who will benefit from intervention. A great deal of work has been done worldwide to improve our knowledge of the genetics behind prostate cancer and the specificity of PSA by developing assays for different PSA isoforms. Common genetic alterations in prostate cancer patients have been identified, including CpG hypermethylation of GSPT1 and TMPRSS2:ERG gene fusion. Serum and urine detection of RNA biomarkers (eg, PCA3) and prostate cancer tissue protein antibodies (eg, EPCA) are being evaluated for detection and prognostic tools. This article reviews some of the promising developments in biomarkers.

Xie, C., et al. (2011). "A novel multiplex assay combining autoantibodies plus PSA has potential implications for classification of prostate cancer from non-malignant cases." Journal of Translational Medicine 9.

Background: The lack of sufficient specificity and sensitivity among conventional cancer biomarkers, such as prostate specific antigen (PSA) for prostate cancer has been widely recognized after several decades of clinical implications. Autoantibodies (autoAb) among others are being extensively investigated as potential substitute markers, but remain elusive. One major obstacle is the lack of a sensitive and multiplex approach for quantifying autoAb against a large panel of clinically relevant tumor-associated antigens (TAA). Methods: To circumvent preparation of phage lysates and purification of recombinant proteins, we identified B cell epitopes from a number of previously defined prostate cancer-associated antigens (PCAA). Peptide epitopes from cancer/testis antigen NY-ESO-1, XAGE-1b, SSX-2,4, as well as prostate cancer overexpressed antigen AMACR, p90 autoantigen, and LEDGF were then conjugated with seroMAP microspheres to allow multiplex measurement of autoAb present in serum samples. Moreover, simultaneous quantification of autoAb plus total PSA was achieved in one reaction, and termed the "A+PSA" assay. Results: Peptide epitopes from the above 6 PCAA were identified and confirmed that autoAb against these peptide epitopes reacted specifically with the full-length protein. A pilot study was conducted with the A+PSA assay using pre-surgery sera from 131 biopsy-confirmed prostate cancer patients and 121 benign prostatic hyperplasia and/or prostatitis patients. A logistic regression-based A+PSA index was found to enhance sensitivities and specificities over PSA alone in distinguishing prostate cancer from nonmalignant cases. The A+PSA index also reduced false positive rate and improved the area under a receiver operating characteristic curve. Conclusions: The A+PSA assay represents a novel platform that integrates autoAb signatures with a conventional cancer biomarker, which may aid in the diagnosis and prognosis of prostate cancer and others.

Xinzhou, H., et al. (2011). "RKIP inhibits the migration and invasion of human prostate cancer PC-3M cells through regulation of extracellular matrix." Molecular Biology 45(6): 921-928.

Raf kinase inhibitor protein (RKIP) plays a pivotal role in several intracellular signaling cascades and has been implicated as a metastasis suppressor in multiple cancer cells including prostate cancer cells, but the mechanism is not very clear. In this study, we investigated the effect of RKIP on cell proliferation, migration and invasion using human prostate cancer PC-3M cells as a model system. Our results indicate that RKIP does not effect cell proliferation in PC-3M cells, but inhibits both cell migration and cell invasion. In association with this inhibitory effect, RKIP down-regulates matrix metalloproteinases (MMP-2 and MMP-9), cathepsin B and urinary plasminogen activator (uPA). Also RKIP has the ability to regulate the expression of E-cadherin. But ectopic expression of RKIP does not affect the level of the Snail protein. As it has been indicated here, RKIP inhibits the migration and invasion ability of human prostate cancer cells through regulation of the extracellular matrix. These findings provide new mechanistic insight how RKIP suppresses metastasis in vitro.

Xinzhou, H., et al. (2011). "RKIp inhibits the migration and invasion of human prostate cancer PC-3M cells through regulation of extracellular matrix." Molekuliarnaia biologiia 45(6): 1004-1011.

Raf kinase inhibitor protein (RKIP) plays a pivotal role in several intracellular signaling cascades and has been implicated as a metastasis suppressor in multiple cancer cells including prostate cancer cells, but the mechanism is not very clear. In this study, we investigated the effect of RKIP on cell proliferation, migration and invasion using human prostate cancer PC-3M cells as a model system. Our results indicate that RKIP does not effect cell proliferation in PC-3M cells, but inhibits both cell migration and cell invasion. In association with this inhibitory effect, RKIP down-regulates matrix metalloproteinases (MMP-2 and MMP-9), cathepsin B and urinary plasminogen activator (uPA). Also RKIP has the ability to regulate the expression of E-cadherin. But ectopic expression of RKIP does not affect the level of the Snail protein. As it has been indicated here, RKIP inhibits the migration and invasion ability of human prostate cancer cells through regulation of the extracellular matrix. These findings provide new mechanistic insight how RKIP suppresses metastasis in vitro.

Yang, S.-I., et al. (2013). "Effects of low-frequency ultrasound combined with microbubbles on benign prostate hyperplasia." Cuaj-Canadian Urological Association Journal 7(11-12): E681-E686.

Introduction: Our objective is to assess the effects of low-frequency ultrasound combined with microbubbles on benign prostate hyperplasia (BPH). Methods: Sixteen Beagle dogs with BPH were randomly assigned into 4 groups (n = 4): control group (without treatment), G1 group (injection with 2 mL of microbubble contrast agent); G2 group (21 kHz ultrasound); and G3 group (injection with 2 mL of microbubble contrast agent + 21 kHz ultrasound). The histopathological damage to prostate cells was assessed via transmission electron microscopy and optical microscopy. The protein expressions of prostate-specific antigen (PSA), inducible nitric oxide synthase (iNOS), superoxide dismutase (SOD) of vessels were detected by enzyme-linked immunosorbent assay (ELISA). Results: Histopathologically, the prostate cells exhibited nuclear chromatin contraction, mitochondrial swelling, degranulation of rough endoplasmic reticulum, basement membrane rupture and cell apoptosis in the G2 and G3 groups; it was especially obvious in the G3 group, while no changes were observed in the control and G1 groups. Although prostate volume using imaging was not significantly changed in all groups after treatment, PSA was significantly reduced in the G2 and G3 groups, and especially obvious in the G3 group (p < 0.05). The iNOS and SOD, which are important oxidative stress factors, significantly increased after treatment in the G2 and G3 groups, but not in the control and G1 groups (p < 0.05). Conclusions: Low-frequency ultrasound is effective in treating BPH; low-frequency ultrasound combined with microbubbles improves the treatment efficacy.

You, J., et al. (2010). "Innovative biomarkers for prostate cancer early diagnosis and progression." Critical Reviews in Oncology Hematology 73(1): 10-22.

The marker currently used for prostate cancer (CaP) detection is an increase in serum prostate-specific antigen (PSA). However, the PSA test which may give false positive or negative information, is not reliable and does not allow the differentiation of benign prostate hyperplasia (BPH), non-aggressive CaP and aggressive CaP. There is thus an urgent need to search for novel CaP biomarkers to improve the early detection and accuracy of diagnosis, determine the aggressiveness of CaP and to monitor the efficacy of treatment. Proteomic techniques allow for a high-throughput analysis of bio-fluids with the visualization and quantification of thousands of potential protein markers and represent very promising tools in the search for new, improved molecular markers of CaP. In this review, we will summarize conventional CaP biomarkers and focus on novel identified biomarkers for CaP early diagnosis and progression that might be used in the future. (C) 2009 Elsevier Ireland Ltd. All rights reserved.

Young, A., et al. (2012). "Correlation of Urine TMPRSS2:ERG and PCA3 to ERG plus and Total Prostate Cancer Burden." American Journal of Clinical Pathology 138(5): 685-696.

ERG rearrangements (most commonly transmembrane protease, serine 2 [TMPRSS2]:ERG [T2:ERG] gene fusions) have been identified in approximately 50% of prostate cancers. Quantification of T2:ERG in postdigital rectal examination urine, in combination with PCA3, improves the performance of serum prostate-specific antigen for prostate cancer prediction on biopsy. Here we compared urine T2:ERG and PCA3 scores with ERG+ (determined with immunohistochemical analysis) and total prostate cancer burden in 41 mapped prostatectomies. Prostatectomies had a median of 3 tumor foci (range, 1-15) and 2.6 cm of summed linear tumor dimension (range, 0.6-7.1 cm). Urine T2 :ERG score correlated most with summed linear ERG+ tumor dimension and number of ERG+ foci (r(s) = 0.68 and 0.67, respectively, both P < .001). Urine PCA3 score showed weaker correlation with both number of tumor foci (r(s), = 0.34, P = .03) and summed linear tumor dimension (r(s) = 0.26, P = .10). In summary, we demonstrate a strong correlation between urine T2:ERG score and total ERG+ prostate cancer burden at prostatectomy, consistent with high tumor specificity.

Yu, E. Y., et al. (2011). "Once-daily Dasatinib: Expansion of Phase II Study Evaluating Safety and Efficacy of Dasatinib in Patients With Metastatic Castration-resistant Prostate Cancer." Urology 77(5): 1166-1171.

OBJECTIVES To determine the activity and tolerability of 100-mg once-daily (QD) dasatinib in patients with metastatic castration-resistance prostate cancer (CRPC). Dasatinib, an oral Src family kinase inhibitor, has demonstrated both preclinical and clinical activity with twice-daily dosing in patients with metastatic CRPC. METHODS Chemotherapy-naive men with metastatic CRPC and increasing prostate-specific antigen levels were treated with dasatinib 100 mg QD. The primary measurement was a composite lack of disease progression, according to the Prostate Cancer Working Group 2 criteria, determined every 12 weeks during the study. The other analyses included changes in the prostate-specific antigen level, bone lesions, soft tissue disease, and bone turnover markers (urine N-telopeptide and bone alkaline phosphatase). RESULTS The present trial was designed before the publication of the recent Prostate Cancer Working Group 2 criteria; however, the analyses are presented to conform to the updated guidelines. A total of 48 patients received dasatinib. A lack of disease progression was observed in 21 patients (44%) at week 12 and in 8 (17%) at week 24. Urine N-telopeptide was reduced by >= 40% from baseline in 22 (51%) of 43 patients, and bone alkaline phosphatase was decreased in 26 (59%) of 44 patients. Dasatinib was well-tolerated, with only 6 patients (13%) with drug-related grade 3-4 adverse events and 3 (6%) with grade 3 adverse events. The most common treatment-related adverse events (>= 20%) were fatigue, nausea, diarrhea, headache, and anorexia. CONCLUSIONS Dasatinib 100 mg QD has a favorable safety profile and maintains a similar degree of activity as the previously reported twice-daily dosing schedules. These data support additional study of dasatinib 100 mg QD for metastatic CRPC. UROLOGY 77: 1166-1171, 2011. (C) 2011 Elsevier Inc.

Yu, E. Y., et al. (2009). "Phase II Study of Dasatinib in Patients with Metastatic Castration-Resistant Prostate Cancer." Clinical Cancer Research 15(23): 7421-7428.

Purpose: Antiproliferative and antiosteoclastic activity from preclinical models show potential for dasatinib, an oral SRC and SRC family kinase inhibitor, as a targeted therapy for patients with prostate cancer. This phase 11 study investigated the activity of dasatinib in patients with metastatic castration-resistant prostate cancer (CRPC). Experimental Design: Chemotherapy-naive men with CRPC and increasing prostate-specific antigen were treated with dasatinib 100 or 70 mg twice daily. Endpoints included changes in prostate-specific antigen, bone scans, measurable disease (Response Evaluation Criteria in Solid Tumor), and markers of bone metabolism. Following Prostate Cancer Working Group 2 guidelines, lack of progression according to Response Evaluation Criteria in Solid Tumor and bone scan was determined and reported at 12 and 24 weeks. Results: Forty-seven patients were enrolled and received dasatinib (initial dose 100 mg twice daily, n = 25; 70 mg twice daily, n = 22), of whom 41 (87%) had bone disease. Lack of progression was achieved in 20 (43%) patients at week 12 and in 9 (19%) patients at week 24. Of 41 evaluable patients, 21 (51%) patients achieved 40% reduction in urinary N-telopeptide by week 12, with 33 (80%) achieving some level of reduction anytime on study. Of 15 patients with elevated urinary N-telopeptide at baseline, 8 (53%) normalized on study. Of 40 evaluable patients, 24 (60%) had reduction in bone alkaline phosphatase at week 12 and 25 (63%) achieved some reduction on study. Dasatinib was generally well tolerated and treatment-related adverse events were moderate. Conclusions: This study provides encouraging evidence of dasatinib activity in bone and reasonable tolerability in chemotherapy-naive patients with metastatic CRPC. (Clin Cancer Res 2009;15(23):7421-8)

Zeng, Y., et al. (2009). "Gene expression Profiles of Lysophosphatidic Acid-Related Molecules in the Prostate: Relevance to Prostate Cancer and Benign Hyperplasia." Prostate 69(3): 283-292.

OBJECTIVE. To elucidate gene expression profiles of lysophosphatidic acid (LPA)-related molecules in cancer, pre-cancerous lesion, and benign hyperplasia of the prostate. MATERIALS AND METHODS. Prostate tissue samples were surgically obtained from 10 patients with localized prostate cancer and seven patients with invasive bladder cancer. Cancer cells and the corresponding stromal cells from normal prostate, high grade intraepithelial neoplasia (HGPIN), benign hyperplastic glands were isolated by laser capture microdissection. mRNA levels of three LPA receptors, LPA1, LPA2, LPA3, two LPA-synthesizing enzymes, autotaxin (ATX), acylglycerol kinase (AGK), and a LPA-degradation enzyme, prostatic acid phosphatase (PAP), were quantitatively assessed. The expression levels of the same genes were also determined in three human prostate cancer cell lines LNCaP, PC-3, and DU-145. RESULTS. LPA1 mRNA level was significantly decreased in HGPIN and cancer epithelia when compared to the benign glands. LPA3 mRNA level was elevated in cancer epithelia compared to benign glands. LPA3, AGK, and PAP were predominantly expressed in LNCaP cells while LPA1 and ATX gene expressions were found in PC-3 and Du-145 cells. In BPH, AGK was abundantly expressed in the stroma while PAP was predominant in epithelial cells. CONCLUSIONS. By acting via LPA3, LPA may play an important role in the development of prostate cancer. Switching of LPA receptor expression from LPA3 to LPA1, may be involved in prostate cancer progression and/or androgen independence. LPA may also play a key role in the development of benign prostatic hyperplasia. Prostate 69:283-292,2009. (C) 2008 Wiley-Liss. Inc.

Zenzmaier, C., et al. (2012). "Phosphodiesterase Type 5 Inhibition Reverts Prostate Fibroblast-to-Myofibroblast Trans-Differentiation." Endocrinology 153(11): 5546-5555.

Phosphodiesterase type 5 (PDE5) inhibitors have been demonstrated to improve lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH). Because BPH is primarily driven by fibroblast-to-myofibroblast trans-differentiation, this study aimed to evaluate the potential of the PDE5 inhibitor vardenafil to inhibit and reverse trans-differentation of primary human prostatic stromal cells (PrSC). Vardenafil, sodium nitroprusside, lentiviral-delivered short hairpin RNA-mediated PDE5 knockdown, sodium orthovanadate, and inhibitors of MAPK kinase, protein kinase G, Ras homolog family member (Rho) A, RhoA/Rho kinase, phosphatidylinositol 3 kinase and protein kinase B (AKT) were applied to PrSC treated with basic fibroblast growth factor (fibroblasts) or TGF beta 1 (myofibroblasts) in vitro, in chicken chorioallantoic membrane xenografts in vivo, and to prostatic organoids ex vivo. Fibroblast-to-myofibroblast trans-differentiation was monitored by smooth muscle cell actin and IGF binding protein 3 mRNA and protein levels. Vardenafil significantly attenuated TGF beta 1-induced PrSC trans-differentiation in vitro and in chorioallantoic membrane xenografts. Enhancementof nitric oxide/cyclic guanosine monophosphate signaling by vardenafil, sodium nitroprusside, or PDE5 knock down reduced smooth muscle cell actin and IGF binding protein 3mRNA and protein levels and restored fibroblast-like morphology in trans-differentiated myofibroblast. This reversal of trans-differentiation was not affected by MAPK kinase, protein kinase G, RhoA, or RhoA/Rho kinase inhibition, but vardenafil attenuated phospho-AKT levels in myofibroblasts. Consistently, phosphatidylinositol 3 kinase or AKT inhibition induced reversal of trans-differentiation, whereas the tyrosine phosphatase inhibitor sodium orthovanadate abrogated the effect of vardenafil. Treatment of prostatic organoids with vardenafil ex vivo reduced expression of myofibroblast markers, indicating reverse remodeling of stroma towards a desired higher fibroblast/myofibroblast ratio. Thus, enhancement of the nitric oxide/cyclic guanosine monophosphate signaling pathway by vardenafil attenuates and reverts fibroblast-to-myofibroblast trans-differentiation, hypothesizing that BPH patients might benefit from long-term therapy with PDE5 inhibitors. (Endocrinology 153: 5546-5555, 2012)

Zhai, X.-L., et al. (2014). "Correlation study between the polymorphism of repetitive sequence in gene CAG of androgen receptor and the occurrence and progression of prostate cancer." Asian Pacific Journal of Tropical Medicine 7(4): 301-304.

Objective: To explore the relation between the polymorphism of repetitive sequence in gene GAG of androgen receptor (AR) and the susceptibility and clinical stages as well as pathological grading of prostate cancer among Han population. Method: Sixty-eight cases with prostate cancer hospitalized in Urinary Surgery Department from Feb. 2010 to Feb. 2012 and 60 healthy cases were chosen as research subjects. Methods of PCR and direct sequencing were adopted to detect DNA sequence of AR gene and the length of repetitive sequence in GAG. Results: The lengths of repetitive sequence in CAG of patients with prostate cancer and healthy people were (22.3 +/- 4.6) and (23.0 +/- 4.9), respectively showing no statistical significance. Comparing length (repetitive sequence of CAG)>22, those with that < 22 suffer a remarkably higher risk of prostate cancer (P<0.05). The number of repetitive sequence in CAG of patients at clinical stage C-D was less than that of patients at stage B, and the number of repetitive sequence in GAG of patients with poorly differentiated prostate cancer was also less than that of patients with moderately and highly differentiated prostate cancer. But there was no statistical significance int the difference (P>0.05); the proportion of patients with length <22 at clinical stage C-D was much larger than that of patients at clinical stage B (P<0.05), and as the aggravation of pathological grading, the proportion of patients with the length <22 was also remarkably increased and there was significant difference between patients with highly differentiated prostate cancer and those with poorly differentiated prostate cancer (P<0.05). Conclusions: There is correlation between the occurrence and development of prostate cancer in Han population and the polymorphism of repetitive sequence in gene GAG of androgen receptor. The less the number of repetitive sequence in CAC is, the higher the risk of prostate cancer will be and the more severe the clinical stage and pathological grading will be.

Zhao, Y., et al. (2014). "Prostate stem cell antigen rs2294008 (C>T) polymorphism and bladder cancer risk: a meta-analysis based on cases and controls." Genetics and Molecular Research 13(3): 5534-5540.

Several published articles have evaluated the association between the prostate stem cell antigen (PSCA) rs2294008 (C>T) polymorphism and bladder cancer risk, but the results remain inconclusive. In order to derive a more precise estimation of the association, we performed a meta-analysis of four case-control studies that included 9617 cases and 16,323 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association. Our meta-analysis showed that, overall, the rs2294008 (C>T) polymorphism was associated with bladder cancer susceptibility (OR = 1.29, 95% CI = 1.20-1.40 for TT vs CC; OR = 1.24, 95% CI = 1.16-1.31 for CT vs CC; OR = 1.25, 95% CI = 1.18-1.33 for TT/CT vs CC; OR = 1.13, 95% CI = 1.06-1.20 for TT vs CT/CC). In the stratified analyses, the risk remained significant for studies of European populations, Asian populations, population-based studies, and hospital-based studies. In conclusion, the results suggest that the PSCA rs2294008 (C>T) polymorphism is a risk factor for bladder cancer development.

Zorba, O. U., et al. (2014). "Association Between Prostate Volume and Red Cell Distribution Width." Luts-Lower Urinary Tract Symptoms 6(1): 52-56.

ObjectivesTo evaluate relation between red cell distribution width (RDW) and benign prostatic hyperplasia (BPH). MethodsThe overall study population consisted of 942 men with lower urinary tract symptoms (LUTS), ranging in age from 60 to 85years old. Patients with disorder or medication that can influence lower urinary tract or erythrocytes were excluded from the study. The relationship between RDW, white blood cell (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and prostate volume, International Prostate Symptom Score (IPSS) were assessed with multivariate linear regression model. Patients were analyzed in four groups stratified according to the quartiles of prostate volume. The one-way analysis of variance (anova) was used to compare RDW, WBC CRP, and ESR between different quartiles of prostate volume. ResultsA graded and independent association of RDW with the prostate volume was identified (P=0.001). RDW was significantly associated with prostate volume in multivariate linear regression model that was adjusted for age and hemoglobin. IPSS was significantly correlated with RDW, CRP and ESR. However significance was lost after adjustment for age and prostate volume. The RDW was significantly associated with the surgical treatment in the multivariate linear regression model that was adjusted for age and prostate volume. ConclusionsA correlation between an increased RDW and prostate volume was suggested by the new data from this study. This relation may be a consequence of inflammatory stress arising from BPH. The significant association between the easy, inexpensive RDW may provide a rational basis to include the RDW in algorithms for surgery risk prediction.