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Prostate Specific Membrane Antigen—A Target for Imaging and Therapy with Radionuclides

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Abstract

Prostate cancer continues to represent a major health problem, and yet there is no effective treatment available for advanced metastatic disease. Thus, there is an urgent need for the development of more effective treatment modalities that could improve the outcome. Because prostate specific membrane antigen (PSMA), a transmembrane protein, is expressed by virtually all prostate cancers, and its expression is further increased in poorly differentiated, metastatic, and hormone-refractory carcinomas, it is a very attractive target. Molecules targeting PSMA can be labelled with radionuclides to become both diagnostic and/or therapeutic agents. The use of PSMA binding agents, labelled with diagnostic and therapeutic radio-isotopes, opens up the potential for a new era of personalized management of metastatic prostate cancer.

Introduction

In developed countries, prostate cancer is the second most frequently diagnosed cancer, and the third most common cause of death from cancer in men (Damber and Aus, 2008). More than 90% of the prostate cancers detected with PSA screening are localized and have commensurately high rates of cure. However, the remaining patients often present with advanced disease despite adherence to PSA screening guidelines. Efforts are underway to find biomarkers for the earlier detection of these types of prostate cancers. New biomarkers are being investigated including sarcosine which is proposed as a new urinary marker for monitoring the presence and extent of prostate cancer (Sreekumar et al., 2009).

Prostate cancer diagnosis is based on examination of histopathological or cytological specimens from the gland. The most common way to obtain tissue for diagnosis is by obtaining multiple biopsies, typically ranging in number from 6 to 18 with the guidance of transrectal ultrasound (TRUS). Specimens are graded according to the Gleason scoring system which assesses the two predominant grades (based on a 1–5 scale) and adds them together resulting in a score that ranges between 2 and 10. More advanced Gleason scores are associated with poor cellular differentiation and androgen independence (i.e., growth even in the absence of androgens such as testosterone).

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The role of imaging in prostate cancer diagnosis and treatment can be divided into tumor localization, staging of disease, and the detection of recurrence (Turkbey et al., 2009). In order to choose the most optimal initial treatment at diagnosis, correct pathologic staging is important. TRUS is widely used to guide biopsy of the prostate gland. For determining the extent of localized disease, magnetic resonance imaging (MRI) is most commonly performed, often with the addition of an endorectal coil. Computed tomography (CT) is performed in patients with higher PSA values to assess the possibility of lymphadenopathy or solid organ involvement (e.g., liver or lung metastases). Bone scintigraphy with a ^{99m}Tc-labelled methylene disphonate (Tc-MDP) is widely used for detecting bone metastases. While, positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG), a marker of glucose metabolism, plays an important role in the clinical management of many cancers, it is not very useful in the early stages of prostate cancer. This is mainly due to the low-level metabolism of most prostate cancers resulting in low uptake of ^{18}F-FDG. However, new PET agents have been developed that are more useful for prostate cancer (Bouchelouche and Oehr, 2008; Bouchelouche et al., 2009). Among these are ^{11}C-acetate and choline labelled with ^{18}F or ^{11}C. ^{18}F-fluoride is a recently rediscovered agent that is useful for detecting bone metastases with greater sensitivity than Tc-MDP and offers the possibility of more reliable quantitation. The exact role of PET in staging, detecting recurrence, assessing prognosis, monitoring therapy, and studying the biology of prostate cancer remains to be further elucidated in large clinical trials.

Treatment options for prostate cancer vary depending on age, disease stage, potential side effects of the treatment, and other medical conditions of the patient. Watchful waiting without immediate treatment can be offered in some older patients who have limited life expectancy or less-aggressive tumors. Surgery, external beam radiation therapy, and brachytherapy can be used for treatment of early-stage prostate cancer. Hormonal therapy, chemotherapy, radiation therapy, or a combination of these can be used to treat metastatic disease or as supplemental therapies in early-stage disease (Damber and Aus, 2008). Prostate cancer usually responds to androgen deprivation therapy but, on average, after 12–18 months, resistance develops. Despite several attempts, the median survival for men with metastatic castrate-resistant prostate cancer is 1–2 years. Novel strategies are in development including new cytotoxic agents, antiproliferative therapies, immune-based agents, and antiangiogenic agents (Lassi and Dawson, 2009).

The management of advanced prostate cancer is challenging because the disease has variable clinical and pathologic behavior. The choice of treatment should be patient-specific and risk-adjusted, aimed at improving cancer control, while reducing the risks of treatment-related complications. There is a growing demand for further individualization of treatment plans, which requires accurate characterization of the location and extent of cancer. This characterization necessitates the optimal use of imaging methods. In recent years much focus has been on the development of personalized medicine in oncology, where pharmaceutical therapies are tailored to the particular characteristics of the individual patient and the tumor. In prostate cancer there is increasing evidence that prostate specific membrane antigen (PSMA) may be a target for both imaging and therapy (Elsasser-Beile et al., 2009a; Bouchelouche and Capala, 2010). Furthermore, modifying the imaging agent by replacing the diagnostic radionuclide with a therapeutic one allows delivery of high doses of lethal radiation to specific tumor sites. This “image and treat” strategy has the potential to be a new and more effective treatment modality in managing prostate cancer (Bouchelouche and Capala, 2010).

Prostate Specific Membrane Antigen

Recently, several markers for prostate cancer have been identified and they include cell surface proteins, glycoproteins, receptors, enzymes, and peptides (Ross et al., 2005). Among biomarkers used for imaging of prostate cancer, PSMA has demonstrated to be an excellent target. PSMA is a type II membrane glycoprotein (100–120 kDa) with an intracellular segment (amino acids 1–18), a transmembrane domain (amino acids 19–43), and an extensive extracellular domain (amino acids 44–750) (Ghosh and Heston, 2004). PSMA is expressed in secretory cells within the prostatic epithelium, and is absent or moderately expressed in most hyperplastic and benign tissue (Elsasser-Beile et al., 2009a). Furthermore, PSMA is highly expressed by virtually all prostate cancers, and the expression increases with tumor aggressiveness, androgen-independence, metastatic disease, and disease recurrence (Ross et al., 2003)

Despite its name, PSMA is also expressed in other tissues besides the prostate. Studies have demonstrated PSMA expression in the small intestine, proximal renal tubules, and salivary glands (Tasch et al., 2001). However, the expression levels in these tissues are much lower than in the prostate gland (Sokoloff et al., 2000). Some minimal expression is also observed in the brain but most agents, particularly antibodies, do not penetrate the brain because of the blood-brain barrier. Furthermore, PSMA is expressed in the neovasculature of numerous other solid tumors, including bladder, pancreas, lung, and kidney cancers, but not in normal vasculature (Elsasser-Beile et al., 2009a). Thus, PSMA may potentially become a target for imaging and therapy in these tumors.

PSMA has two unique enzymatic functions, folate hydrolase and NAALADase (cleaving terminal glutamate from the neurodipeptide, N-acetyl-aspartyl-glutamate, NAAG) (Ghosh and Heston, 2004). NAAG is concentrated in neuronal synapses while folylpoly-γ-glutamates are present in dietary components. PSMA protein (folate hydrolase), located in the brush border surface of small intestine, enables the generation of folates and subsequent folate uptake. The apparent low levels of PSMA expression in the small intestine and salivary glands are most likely related to these biochemical activities. However, the specific biochemical function of PSMA in prostate tissue and the reason for its elevation in prostate cancer remains unclear. In contrast to other highly restricted prostate-related antigens, like the prostate specific antigen (PSA) and prostatic acid phosphatase, PSMA is not a secretory protein (Troyer et al., 1995). PSMA, like other cell surface receptors, undergoes internalization constitutively, and the constitutive internalization of PSMA may reflect the recycling of a structural protein or may be mediated by binding of a ligand (Ghosh and Heston, 2004). However, at present no naturally-occurring PSMA ligand is known.

The unique expression of PSMA makes it an important marker of prostate cancer. Furthermore, PSMA represents a large extracellular target for imaging agents, and for therapeutic agents such as radionuclides or other therapeutic strategies including immunotoxins, retargeting of immune cells, pro-drug activation, PSMA vaccines, and plasmid DNA and adenoviral immunizations (Elsasser-Beile et al., 2009a). PSMA is an excellent target for radionuclide imaging and therapy of prostate cancer for several reasons. PSMA is (1) mainly expressed in the prostate, (2) highly expressed at all stages of the disease, (3) upregulated in androgen-insensitive or metastatic disease, (4) expressed on the cell surface as an integral membrane protein, and not released into the circulation, and (5) internalized after antibody binding (receptor-mediated endocytosis).

Imaging of Prostate Specific Membrane Antigen

The first clinical agent targeting PSMA in prostate cancer was ProstaScint® (capromab pendetide, EUSA Pharma) (Elsasser-Beile et al., 2009a). ProstaScint is an FDA approved

imaging agent for prostate cancer that has been in use since the late 1990s. It consists of an intact murine monoclonal antibody, 7E11-C5.3 (mAb 7E11), labelled with ^{111}In via a linker chelator—GYK-DTPA-HCL (Apolo et al., 2008). The overall sensitivity and specificity of ProstaScint® for detecting prostate cancer have varied in reported studies, with an average sensitivity of 60%, specificity of 70%, positive predictive value of 60%, and negative predictive value of 70% (Apolo et al., 2008). The relatively poor results of the initial studies using mAB 7E11 for radionuclide imaging of prostate cancer might be due to the fact that the antibody recognizes an internal epitope of PSMA requiring that the agent internalize prior to binding. Thus, only cells with damaged cell membranes (e.g., apoptotic or necrotic cells) will bind mAB 7E11, greatly limiting the sensitivity of the agent (Troyer et al., 1997). Recently, ^{111}In-capromab pendetide was used for single photon emission computed tomography (SPECT)/CT imaging of prostate cancer (Seo et al., 2009). The results indicate that ^{111}In-capromab pendetide may have a role in prostate cancer imaging because of the higher sensitivity of modern SPECT/CT cameras and improved resolution of SPECT/CT compared with projection scintigraphy. However, the study was small and larger patient populations are needed to confirm the results.

More recently, radiolabeled mAbs that bind to the *extracellular* domain of PSMA have been developed. These second-generation PSMA-binding antibodies may prove to be superior to capromab pendetide. Among these, the humanized version of the monoclonal antibody J591 has provided promising results in imaging prostate cancers, including bone metastases. J591 had been extensively studied in preclinical models, and it demonstrated high tumor-to-normal tissue ratio in prostate cancer xenografts. Clinical trials using J591 labelled with ^{99m}Tc (^{99m}Tc-labelled J591) demonstrated the detection of primary prostate cancer, but also detected prostate bed recurrence and distant metastases, including bone metastases (Nargund et al., 2005). J591 labelled with therapeutic radionuclides for radioimmunotherapy (RIT) confirmed its utility as a prostate cancer-targeting agent (Bouchelouche et al., 2009).

Several other mAbs that target PSMA for molecular imaging have been developed. Among these new antibodies, three IgG mAbs—3/A12, 3/E7, and 3/F11—have affinity to PSMA (Elsasser-Beile et al., 2006). It has been demonstrated that 3/A12, 3/E7, and 3/F11 bind to different extracellular epitopes of PSMA (Wolf et al., 2009). Results of a recent study, using ^{64}Cu-3/A12 for PET imaging of prostate cancer xenografts, showed good tumor-to-background ratio (Elsasser-Beile et al., 2009b). Another new mAb, 3C6, targeting the extracellular epitope of PSMA has been labelled with ^{111}In for imaging of prostate cancer (Regino et al., 2009).

A disadvantage of full monoclonal antibodies is the slow clearance and uptake resulting in delayed imaging. From a practical standpoint it is more difficult to conduct a test that requires the patient to return for the scan part 48–72 hours after injection than to conduct one that can be performed in one day. Low-molecular-weight, radiopharmaceutical-based imaging agents may provide superior pharmacokinetics for imaging than radiolabelled antibodies. Recently, this small-molecule approach has resulted in the development of a new class of PSMA targeting agents for PET/CT and SPECT/CT imaging. Radiolabelled PSMA inhibitor N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-S-[^{11}C]methyl-l-cysteine (DCFBC) has been successfully used for PET imaging of xenografts that express PSMA (Foss et al., 2005). This work has been extended by preparing and testing a PSMA inhibitor of the same class labelled with ^{18}F (Mease et al., 2008). Biodistribution and imaging studies showed high uptake of ^{18}F-DCFBC in the PSMA positive tumors with little to no uptake in PSMA negative tumors. Urea-based compounds may also present promising agents for prostate cancer imaging with SPECT and PET (Chen et al., 2008). Two small-molecule inhibitors targeting PSMA, MIP-1072 and MIP-1095, have exhibited high affinity for PSMA (Hillier et al., 2009). The uptake of ^{123}I-MIP-1072 and ^{123}I-MIP-1095 in prostate cancer xenografts

was successfully imaged by SPECT/CT. Phosphoramidates may also become a new class of PSMA inhibitors. Recently, ^{18}F-phosphoramidate peptidomimetic was used for in vivo PET imaging studies of prostate cancer xenografts (Lapi et al., 2009).

Prostate Specific Membrane Antigen Endoradiotherapy

Since no effective treatment for advanced metastatic prostate cancer is available, there is an urgent need to develop new therapeutic strategies. The most important alternative to conventional anti-cancer therapy is targeted tumor therapy using molecules that direct anti-cancer drugs specifically to the tumor and, thereby, preventing damage to healthy tissue. For targeted therapy, peptides and antibodies possess desirable features as drug delivery vectors. Endoradiotherapy using peptides or antibodies as targeting moieties combines the favorable targeting properties of these ligands with the biologic effects of high linear energy transfer (LET) radiation as is seen with alpha and beta particles. Another advantage of endoradiotherapy is that smaller amounts of drug can be used as compared to conventional anti-cancer therapy. Furthermore, these drugs can be labelled not only with therapeutics nuclides but also with diagnostic ones. Thus, it is possible to perform imaging and dosimetry of the compound prior to the treatment. The effect of the radionuclide is not only restricted to the targeted cell. The radiation emitted by beta-emitting isotopes is cytotoxic for cells nearby to the targeted cell. This effect is called the “bystander” or “crossfire” effect. This may be important in tumors with a heterogeneous antigen or receptor expression or insufficient vascularization. The therapeutically effective radiation dose is determined by the physical characteristics of the radionuclide administered in endoradiotherapy, and the appropriate volume of tumor cell death can be modulated depending on the range of the radiation emitted.

Several types of radionuclides are suitable for endoradiotherapy. However, the choice of nuclide is very important to its ultimate effectiveness. There are three major groups of therapeutic radionuclides: β-particle emitters (^{67}Cu, ^{90}Y, ^{131}I, ^{177}Lu, ^{186}Re, and ^{188}Re), Auger electron emitters (^{111}In and ^{125}I), and α-particle emitters (^{211}At, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th). The most common radionuclides for endoradiotherapy are ^{131}I, ^{177}Lu, and ^{90}Y. Emitters of lower-energy electrons, such as ^{177}Lu, are useful for treatment of small tumors, while emitters of higher-energy electrons, such as ^{90}Y, are more suitable for larger tumors. Radionuclide therapy is a potentially powerful treatment strategy to eradicate disseminated tumor cells and small metastases. In contrast, bulky tumors and large metastases will likely have to be treated with other modalities such as surgery, external radiation therapy, or chemotherapy before the remaining tumor cells might be effectively treated with radionuclide therapy.

Advanced prostate cancer represents an excellent target for RIT for several reasons: (1) the prostate is a nonvital organ, thereby allowing targeting of tissue-specific antigens, (2) metastases predominantly involve lymph nodes and bones (good access and penetration to circulating antibodies), (3) the metastases are typically small in size allowing good antibody access and penetration, and (4) the serum biomarker PSA (or other newly tested biomarkers) may be used for therapy monitoring. The first studies using the PSMA mAb 7E11/CYT-356 for imaging and RIT of prostate cancer were disappointing (David et al., 2006; Deb et al., 1996). This is due to the fact that the antibody targets an intracellular epitope of PSMA and, therefore, binds only to permeabilized, necrotic cells. In contrast, the mAb J591, which is specifically targeting epitopes located on the external domain of PSMA, binds to both intact and permeabilized cells. J591, labelled with radionuclides such as ^{90}Y and ^{177}Lu has been tested in vitro, in vivo, and recently in clinical trials. In a phase I trial of ^{90}Y-J591 in prostate cancer patients, treatment was well tolerated, and some biologic activity, including objective responses and reduction in PSA, were observed (Milowsky et al., 2004). In a

subsequent trial of ^{177}Lu-J591, a decrease and stabilization of PSA level was observed in 4/35 (11%) and 16/35 (46%) of treated patients, respectively (Bander et al., 2005). ^{177}Lu-J591 may be better suited to small volume prostatic disease, and ^{90}Y-J591 to larger volume disease, although this requires confirmation in larger trials. It has been demonstrated that multiple doses of 30 mCi/m^2 are well tolerated, and excellent targeting of known sites of prostate cancer metastases is possible. Both bone and soft-tissue metastases are targeted by the antibody as seen on ^{111}In-J591 scans (Pandit-Taskar et al., 2008). In a recent phase II trial, a single dose ^{177}Lu-J591 was well tolerated with reversible myelosuppression, and demonstrated anti-tumor activity in patients with progressive metastatic castrate-resistant prostate cancer (Tagawa et al., 2008). Excellent targeting of known sites of metastases was seen in 31 of 32 (97%) patients with a trend for better response with more intense imaging signal.

Conclusions

Prostate cancer is the most common malignancy in men, and a significant proportion of patients diagnosed with prostate cancer progress to advanced metastatic disease. Since no effective treatment of advanced disease exists, new therapeutic modalities are urgently needed. Imaging plays an important role in prostate cancer staging and in the detection of metastasis. The transmembrane protein PSMA is an attractive target because of its overexpression on prostate cancer cells. Results of the recent preclinical and clinical studies have been promising and, in the future, personalized medicine using PSMA as a target for imaging and therapy with radionuclides may become a new treatment strategy for prostate cancer. However, considerable preclinical research effort and clinical studies with a larger number of patients are needed before personalized medicine can be widely used in the routine management of prostate cancer patients.

References

Apolo AB, Pandit-Taskar N, Morris MJ. Novel tracers and their development for the imaging of metastatic prostate cancer. J Nucl Med. 2008; 49:2031–2041. [PubMed: 18997047]

Bander NH, Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ. Phase I trial of 177lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. J Clin Oncol. 2005; 23:4591–4601. [PubMed: 15837970]

Bouchelouche K, Capala J. “Image and treat” - An individualized approach to urological tumors. Curr Opin Oncol. 2010 (in press).

Bouchelouche K, Capala J, Oehr P. Positron emission tomography/computed tomography and radioimmunotherapy of prostate cancer. Curr Opin Oncol. 2009; 21:469–474. [PubMed: 19535981]

Bouchelouche K, Oehr P. Positron emission tomography and positron emission tomography/computerized tomography of urological malignancies: an update review. J Urol. 2008; 179:34–45. [PubMed: 17997425]

Chen Y, Foss CA, Byun Y, Nimmagadda S, Pullambhatla M, Fox JJ, Castanares M, Lupold SE, Babich JW, Mease RC, Pomper MG. Radiohalogenated Prostate-Specific Membrane Antigen (PSMA)-Based Ureas as Imaging Agents for Prostate Cancer. J Med Chem. 2008; 51:7933–43. [PubMed: 19053825]

Damber JE, Aus G. Prostate cancer. Lancet. 2008; 371:1710–1721. [PubMed: 18486743]

David KA, Milowsky MI, Kostakoglu L, Vallabhajosula S, Goldsmith SJ, Nanus DM, Bander NH. Clinical utility of radiolabeled monoclonal antibodies in prostate cancer. Clin Genitourin Cancer. 2006; 4:249–256. [PubMed: 16729907]

Deb N, Goris M, Trisler K, Fowler S, Saal J, Ning S, Becker M, Marquez C, Knox S. Treatment of hormone-refractory prostate cancer with 90Y-CYT-356 monoclonal antibody. Clin Cancer Res. 1996; 2:1289–1297. [PubMed: 9816299]

Elsasser-Beile U, Buhler P, Wolf P. Targeted therapies for prostate cancer against the prostate specific membrane antigen. Curr Drug Targets. 2009a; 10:118–125. [PubMed: 19199907]

Elsasser-Beile U, Reischl G, Wiehr S, Buhler P, Wolf P, Alt K, Shively J, Judenhofer MS, Machulla HJ, Pichler BJ. PET imaging of prostate cancer xenografts with a highly specific antibody against the prostate-specific membrane antigen. J Nucl Med. 2009b; 50:606–611. [PubMed: 19289418]

Elsasser-Beile U, Wolf P, Gierschner D, Buhler P, Schultze-Seemann W, Wetterauer U. A new generation of monoclonal and recombinant antibodies against cell-adherent prostate specific membrane antigen for diagnostic and therapeutic targeting of prostate cancer. Prostate. 2006; 66:1359–1370. [PubMed: 16894535]

Foss CA, Mease RC, Fan H, Wang Y, Ravert HT, Dannals RF, Olszewski RT, Heston WD, Kozikowski AP, Pomper MG. Radiolabeled small-molecule ligands for prostate-specific membrane antigen: in vivo imaging in experimental models of prostate cancer. Clin Cancer Res. 2005; 11:4022–4028. [PubMed: 15930336]

Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004; 91:528–539. [PubMed: 14755683]

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, Zimmerman CN, Barrett JA, Eckelman WC, Pomper MG, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009; 69:6932–6940. [PubMed: 19706750]

Lapi SE, Wahnishe H, Pham D, Wu LY, Nedrow-Byers JR, Liu T, Vejdani K, VanBrocklin HF, Berkman CE, Jones EF. Assessment of an 18F-labeled phosphoramidate peptidomimetic as a new prostate-specific membrane antigen-targeted imaging agent for prostate cancer. J Nucl Med. 2009; 50:2042–2048. [PubMed: 19910433]

Lassi K, Dawson NA. Emerging therapies in castrate-resistant prostate cancer. Curr Opin Oncol. 2009; 21:260–265. [PubMed: 19363343]

Mease RC, Dusich CL, Foss CA, Ravert HT, Dannals RF, Seidel J, Prideaux A, Fox JJ, Sgouros G, Kozikowski AP, Pomper MG. N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: a new imaging probe for prostate cancer. Clin Cancer Res. 2008; 14:3036–3043. [PubMed: 18483369]

Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ, Bander NH. Phase I trial of yttrium-90-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer. J Clin Oncol. 2004; 22:2522–2531. [PubMed: 15173215]

Nargund V, Al HD, Kumar P, Gordon S, Otitie U, Ellison D, Carroll M, Baithun S, Britton KE. Imaging with radiolabelled monoclonal antibody (MUJ591) to prostate-specific membrane antigen in staging of clinically localized prostatic carcinoma: comparison with clinical, surgical and histological staging. BJU Int. 2005; 95:1232–1236. [PubMed: 15892807]

Pandit-Taskar N, O'Donoghue JA, Morris MJ, Wills EA, Schwartz LH, Gonen M, Scher HI, Larson SM, Divgi CR. Antibody mass escalation study in patients with castration-resistant prostate cancer using 111In-J591: lesion detectability and dosimetric projections for 90Y radioimmunotherapy. J Nucl Med. 2008; 49:1066–1074. [PubMed: 18552139]

Regino CA, Wong KJ, Milenic DE, Holmes EH, Garmestani K, Choyke PL, Brechbiel MW. Preclinical evaluation of a monoclonal antibody (3C6) specific for prostate-specific membrane antigen. Curr Radiopharm. 2009; 2:9–17. [PubMed: 20047017]

Ross JS, Gray KE, Webb IJ, Gray GS, Rolfe M, Schenkein DP, Nanus DM, Millowsky MI, Bander NH. Antibody-based therapeutics: focus on prostate cancer. Cancer Metastasis Rev. 2005; 24:521–537. [PubMed: 16408160]

Ross JS, Sheehan CE, Fisher HA, Kaufman RP Jr, Kaur P, Gray K, Webb I, Gray GS, Mosher R, Kallakury BV. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003; 9:6357–6362. [PubMed: 14695135]

Seo Y, Aparici CM, Cooperberg MR, Konety BR, Hawkins RA. In vivo tumor grading of prostate cancer using quantitative 111In-capromab pendetide SPECT/CT. J Nucl Med. 2009; 51:31–36. [PubMed: 20008977]

Sokoloff RL, Norton KC, Gasior CL, Marker KM, Grauer LS. A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine. Prostate. 2000; 43:150–157. [PubMed: 10754531]

Sreekumar A, Poisson LM, Rajendiran TM, Khan AP, Cao Q, Yu J, Laxman B, Mehra R, Lonigro RJ, Li Y, et al. Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression. Nature. 2009; 457:910–914. [PubMed: 19212411]

Tagawa ST, Jeske S, Milowski MI, Vallabahajosula S, Goldsmith SJ, Matulich D, Kaplan I, Bander NH, Nanus DM. Phase II trial of 177Lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (177Lu-J591) in patients with metastatic castrate-resistent prostate cancer. Cancer Biother Radiopharm. 2008; 23(4):525 (abstract).

Tasch J, Gong M, Sadelain M, Heston WD. A unique folate hydrolase, prostate-specific membrane antigen (PSMA): a target for immunotherapy? Crit Rev Immunol. 2001; 21:249–261. [PubMed: 11642607]

Troyer JK, Beckett ML, Wright GL Jr. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. Int J Cancer. 1995; 62:552–558. [PubMed: 7665226]

Troyer JK, Beckett ML, Wright GL Jr. Location of prostate-specific membrane antigen in the LNCaP prostate carcinoma cell line. Prostate. 1997; 30:232–242. [PubMed: 9111600]

Turkbey B, Pinto PA, Choyke PL. Imaging techniques for prostate cancer: implications for focal therapy. Nat Rev Urol. 2009; 6:191–203. [PubMed: 19352394]

Wolf P, Freudenberg N, Buhler P, Alt K, Schultze-Seemann W, Wetterauer U, Elsasser-Beile U. Three conformational antibodies specific for different PSMA epitopes are promising diagnostic and therapeutic tools for prostate cancer. Prostate. Nov 24.2009 [Epub ahead of print].