Prostate-specific membrane antigen-based imaging

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Abstract

Prostate cancer (CaP) is the most common noncutaneous malignancy affecting men in North America. Despite significant efforts, conventional imaging of CaP does not contribute to patient management as much as imaging performed for other common cancers. Given the lack of specificity in conventional imaging techniques, one possible solution is to screen for CaP-specific antigenic targets and generate agents able to specifically bind. Prostate-specific membrane antigen (PSMA) is overexpressed in CaP tissue, with low levels of expression in the small intestine, renal tubular cells, and salivary gland. The first clinical agent for targeting PSMA was 111In-capromab, involving an antibody recognizing the internal domain of PSMA. The second- and third-generation humanized PSMA binding antibodies have the potential to overcome some of the limitations inherent to capromab penditide (i.e., inability to bind to live CaP cells). One example is the humanized monoclonal antibody J591 (Hu mAb J591) that was developed primarily for therapeutic purposes but also has interesting imaging characteristics, including the identification of bone metastases in CaP. The major disadvantage of use of mAb for imaging is slow target recognition and background clearance in an appropriate time frame for diagnostic imaging. Urea-based compounds, such as small molecule inhibitors may also present promising agents for CaP imaging with single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Two such small-molecule inhibitors targeting PSMA, MIP-1072, and MIP-1095 have exhibited high affinity for PSMA. The uptake of 123I-MIP-1072 and 123I-MIP-1095 in CaP xenografts have imaged successfully with favorable properties amenable to human trials. While advances in conventional imaging will continue, Ab and small molecule imaging exemplified by PSMA targeting have the greatest potential to improve diagnostic sensitivity and specificity. © 2012 Elsevier Inc. All rights reserved.

Keywords: Prostate-specific membrane antigen; Prostate cancer; Molecular imaging; Monoclonal antibody; Single-photon emission computed tomography; Positron emission tomography

1. Introduction

Prostate cancer (CaP) is the most common noncutaneous malignancy affecting men in North America. In 2011, approximately 240,890 patients were diagnosed with CaP and 33,720 died of the disease in the USA [1]. The large majority of CaP cases have clinically localized low-risk disease and high cure rates. The remaining patients present with advanced disease that is not completely characterized by standard-of-care clinical algorithms or conventional imaging. There is a considerable interest in developing an accurate noninvasive imaging biomarker that will ideally quantify aggressiveness, extent, and burden of disease.

The role of imaging in CaP is divided into detection of recurrent and/or metastatic disease and lesion localization [2]. Despite significant efforts, conventional imaging of CaP does not contribute to patient management as much as imaging performed for other common cancers. In addition, these imaging tests yield little information to differentiate aggressive from indolent disease. The first postdiagnostic imaging test is often an extent-of-disease evaluation with magnetic resonance imaging (eMRI-en-
dorectal coil) or computed tomography (CT) to evaluate the prostate and/or prostate bed, locoregional lymphadenopathy, solid organ, or bony involvement in high-risk patients. Bone scintigraphy with $^{99m}$Tc-MDP or more recently, $^{18}$F-NaF is widely used as an adjunct for the detection of bone metastases. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has no role in early diagnosis of CaP because of low and heterogeneous utilization of glucose by CaP, and it has a limited role in late stage cancers [3]. Other nonspecific PET agents, such as acetate and choline ($^{11}$C and $^{18}$F-labeled) or MR-based nanoparticles, diffusion weighted imaging, and spectroscopy may have a future role; however, the performance of these agents remains to be determined in randomized controlled clinical trials.

2. Antigen-based imaging

Given the lack of specificity in conventional imaging techniques, one possible solution is to screen for CaP-specific antigenic targets and develop agents capable of specific binding. In the case of CaP, initial attempts began in the 1980s with monoclonal antibodies (mAbs) to prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) [4]. While the relevance and specificity of these antigens is appropriate, PSA and PAP are secreted antigens precluding cell-associated antibody binding. Furthermore, the presence of PSA and PAP in plasma effectively blocks specific antibody binding at the tumor site.

One future direction in CaP imaging involves the development of imaging biomarkers and the exploitation of existing biomarkers to improve the accuracy of detecting prostate disease at every stage. Recently, various markers of CaP have been identified, which includes cell surface proteins, glycoprotein, receptors, enzymes, and peptides [5]. Prostate-specific membrane antigen (PSMA) is the most well established, highly specific prostate epithelial cell membrane antigen known [6–10]. Pathology studies have indicated that virtually all CaP express PSMA [11–14]. The expression of PSMA increases progressively in higher-grade cancers, metastatic disease, and castration-resistant prostate cancer (CRPC) [8,15–17].

3. Prostate-specific membrane antigen imaging

Despite its name, PSMA is expressed in other tissues, including normal (benign) prostate epithelium, the small intestine, renal tubular cells, and salivary gland [18,19]. This “nontarget” expression is fortunately 100- to 1,000-fold less than baseline expression in CaP [10]. Furthermore, antibodies generally do not cross intact basement membrane and tight junctions required to access these sites of non-CaP PSMA expression. Unlike other prostate-specific antigens like PSA, PSMA is not secreted and is membrane bound [9]. The unique functional characteristics, CaP specificity, and antigenic access make PSMA an ideal extracellular target for various imaging (Table 1) and therapeutic agents.

4. Monoclonal antibody targeting of PSMA expression

PSMA has several optimal characteristics for targeting by antibodies. First, it is a highly expressed prostate-restricted nonsecreted protein anchored to the plasma membrane. Second, its expression increases as tumor grade increases with concurrent increases in metastatic sites and CRPC [20]. In addition, the 19 amino acid cytoplasmic domain contains a novel MXXXL internalization motif resulting in its internalization and endosomal recycling which increases the deposition of conjugated radiometals into the cell. This last quality potentially improves both imaging and therapeutic efficacy [21].

5. PSMA-intracellular epitope imaging

The first clinical agent for targeting PSMA in CaP was $^{111}$In-capromab [22]. It consists of a murine antibody 711E-C5.3 (mAb7E11) labeled with $^{111}$In. This mAb had affinity directed against the short intracellular epitope of the protein (amino acids 1–18) and was developed for presurgical staging and the evaluation of PSA relapse after local therapy. In presurgical patients with high-risk disease, but negative conventional imaging, capromab penditide was able to identify a subset of patients with occult local nodal disease. It was assumed that this upstaging of disease and sparing of unnecessary surgery would lead to diverging outcomes, but no studies have been performed to determine whether high risk patients with negative capromab scans fare better. In fact, capromab penditide scans fail to image bone metastases, which are frequently the initial site of metastasis in 72% of patients on can assume a significant false negative rate in the setting of PSA relapse [23]. These findings highlight the main controversy with capromab detection. It has shown a varied amount of efficacy with an average sensitivity and specificity of 60% and 70%, respectively [24]. The poor efficacy associated with radionuclide imaging has been associated to binding of mAb7E11 to a receptor located inside the CaP cell. Thus, only nonviable cells who have damaged cell membranes bind mAb7E11, which limits its use as a good imaging agent [25]. Capromab use in single-photon emission computed tomography (SPECT) study suggested that higher sensitivities can be obtained, but with persistent limitations in detection of bone metastases [22]. A promising next generation antibody (JS91) that targets the extracellular domain of PSMA may provide significant benefits to the imaging of CaP.
6. PSMA-extracellular epitope imaging

The second- and third-generation humanized PSMA binding antibodies have the potential to overcome some of the limitations inherent to capromab penditide. One example is the humanized monoclonal antibody J591 (hereafter referenced as J591) that was developed primarily for therapeutic purposes but also has interesting imaging characteristics, including the identification of bone metastases in CaP [26]. J591 has been studied extensively.

<table>
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<td>Hu mAb J591.</td>
<td>Extracellular domain of PSMA.</td>
<td>$^{111}$In, $^{90}$Y, $^{177}$Lu.</td>
<td>PSMA-specific internalizing antibodies, such as J591 and J415 are ideal mAbs for the development of novel therapeutic methods to target the delivery of beta-emitting radionuclides, which include $^{131}$In, $^{90}$Y, and $^{177}$Lu for the treatment of PSMA-positive tumors [27].</td>
<td>J591 is specific to external domain of PSMA, thus targeting viable tumor. These immunoconjugates are better candidates for both imaging and targeted therapy than are antibodies targeting PSMA internally.</td>
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sively in preclinical models where it has demonstrated excellent binding characteristics and tumor-to-background signal in CaP xenografts. It has been demonstrated that PSMA-specific internalizing antibodies, such as J591 and J415, may be the ideal mAbs for the development of novel therapeutic methods to target the delivery of beta-emitting radionuclides, which include 131I, 90Y, and 177Lu for the treatment of PSMA-positive tumors suggesting possible applications in imaging and targeted radiation therapy. In addition, J591 is specific to external domain of PSMA, thus targeting viable tumor. These immunocytocides are better candidates for both imaging and targeted therapy than are antibodies targeting PSMA internally.

In addition to J591, three additional mAbs (3/A12, 3/E7, and 3/F11) have been characterized [28]. These three IgG mAbs bind to different epitopes of the extracellular domain and have slightly different pharmacokinetics, but all have some potential for future development [29]. These antibodies (3/A12 in particular) are labeled with 64Cu and have demonstrated good in vivo tumor-to-background ratios required in a PET ligand [30]. Another new mAb, 3C6, targeting the extracellular epitope of PSMA has been labeled with 111In-for the imaging of CaP xenografts and eventually patients in a clinical setting [31]. Furthermore, antibody fragments and minibodies are in development for immunoPET imaging.

7. PSMA-small molecule inhibitors

The major disadvantage of use of mAb for imaging is slow target recognition and background clearance in an appropriate time frame for diagnostic imaging. In general, radiopharmaceuticals that have thrived in the clinic
have superior safety profiles, low radiation dose, and allow for administration and imaging in the same day. Based in part on homology to the PSMA receptors enzymatic moiety to NAALDase, Maresca et al. described the design and synthesis of a series of small molecule inhibitors of PSMA with the potential to image CaP with improved pharmacokinetics [32]. To this end, radiolabeled PSMA inhibitor N\{(S)-1,3-dicarboxypropyl\} carbamoyl-S-[11C]methyl-l-cysteine (DCFBC) has been successfully used for PET imaging of human PSMA expressing xenografts [33]. This work has been extended by preparing and testing a PSMA inhibitor of the same class labeled with $^{18}$F [34]. Biodistribution and imaging studies showed high uptake of $^{18}$F-DCFBC in PSMA positive with little to no uptake in PSMA negative tumors. Urea-based compounds may also present promising agents for CaP imaging with SPECT and PET [35]. Two such urea-based small-molecule inhibitors targeting PSMA, MIP-1072 and MIP-1095, have exhibited high affinity for PSMA [36]. The uptake of $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 in CaP xenografts have imaged successfully with favorable properties amenable to human trials.

Functionally, PSMA is a proteolytic enzyme with high affinity to $\gamma$-glutamyl folic acid derivatives and N-acetylaspartylglutamate, as well as dipeptides similar to these compounds. Another class of PSMA inhibitors was created by utilizing and editing the above reference dipeptide motif and systematically pruning the molecule to pseudo-irreversibly bind to PSMA (Fig. 1).

These phosphoramidates localize, bind, and internalize in PSMA-positive cells in vitro and have been fluorinated to function as a PET tracer in a murine xenograft model, and biodistribution data in murine xenografts has been reported [37].

8. Clinical role of PSMA targeted imaging

8.1. $^{111}$In-capromab imaging of metastatic disease

The initial excitement following capromab imaging was that it would detect sites of soft tissue primary disease and help in presurgical staging following biochemical relapse. The following clinical studies were designed in the context of standard-of-care management to assess performance in defined cases where the sensitivity, specificity, and positive/negative predictive value could be ethically determined.

In a clinical trial, radioimmunoscintigraphy localized residual or metastatic CaP in 15 patients after prostatectomy and lymphadenectomy for CaP with rising serum PSA. All patients had negative pre-study radiographic abdominal and pelvic cross-sectional images, and there were no adverse effects related to $^{111}$In-capromab pentitide infusion and little human antimouse antibody response [38]. An additional study with 7E11 radiolabeled with indium and therapeutic nuclide $^{90}$Y demonstrated a similar relationship with conventional imaging in patients with known metastatic CaP [39].

8.2. $^{111}$In-capromab in patients with biochemical relapse and negative conventional imaging

Although $^{111}$In-capromab failed to detect many of the bone scan positive lesions and CT positive soft tissue lesions, there are somewhat counterintuitive successes of capromab in the setting of otherwise negative imaging. These studies include patients who have a lower burden and prevalence of disease. The main 2 clinical settings are presurgical staging and postsurgical PSA relapse. In the presurgical studies, capromab and surgical pathology
of resected lymph nodes were compared with no attempt to identify possible bony lesions. In studies on high-risk patients (high presurgical PSA, high Gleason score/clinical stage) capromab’s performance was significantly better than CT scans. In this study, 152 patients (64/152 with positive nodes on pathology) capromab scans showed a sensitivity of 62%, specificity of 72%, PPV of 62%, NPV of 2%, and an overall accuracy of 68% [40]. In comparison, CT had sensitivity of 4% and specificity of 100%. Interestingly, the 62% sensitivity in these soft tissue lesions that are too-small-to-characterize lesions on CT/MR is similar to the sensitivity is the large lesions in the metastatic PC studies. This would suggest that the main indication for 111In-capromab is to detect diminutive soft tissue lesions. Once the lesions are large or within the bones, the advantage disappears as anatomic imaging becomes more relevant. Improved visualization of these scintigraphic findings by improved radiotracer detection or a mAb affinity would increase the relevance of PSMA imaging dramatically.

8.3. 111In-capromab in extent-of-disease analysis

The second relevant clinical setting for capromab imaging is distinguishing local vs. systemic extent-of-disease in patients with a PSA relapse after radical prostatectomy. Approximately 30% of patients develop PSA relapse following prostatectomy face the clinical dilemma of whether to initiate salvage external beam radiotherapy (EBRT) to the prostate bed or opt for systemic therapy. This quandary exists because to date there is no reliable way to determine extent-of-disease on relapse in CaP (Table 2).

In part because of the availability of PSA to reliably monitor for early recurrence, unlike many other cancers, MRI and CT ± PET are usually not the initial diagnostic test detecting recurrence, and are unreliable modality to determine the extent of disease. In a study of 32 men with residual biochemical evidence of disease after radical prostatectomy, Kahn et al. used capromab scans to attempt to identify men most likely to have EBRT-induced PSA response [41]. Capromab scans demonstrated metastasis in 9/32 (28%) with disseminated disease and 23/32 with local disease. Of the patients with local disease, 61% had a durable EBRT response, whereas only 22% with disseminated disease had a similar response. This result was highly suggestive of a role for capromab for extent-of-disease selection. However, the size of the cohorts and questions about how similar the groups of responders and nonresponder were, continue to plague this study.

Another study by Levesque et al. produced similar results, suggesting that capromab is useful in selecting patients for salvage EBRT [42]. Unfortunately, other studies have been contradictory. In Wilkinson’s study, 42 patients had rising PSA levels after prostatectomy and 15/42 had limited disease. Unlike the prior studies, only 7/14 (42%) had a durable PSA response at follow-up [43]. Similarly, Thomas and Chodak conducted a study with 192 patients. Thirty of them received salvage radiotherapy (RT) but there was no statistically significant difference between the findings of the capromab scan and the likelihood of responding to salvage RT [44].

8.4. 111In-capromab SPECT/CT imaging

Recent studies have focused on the use of 111In-capromab SPECT/CT fusion imaging and/or fusion of SPECT images with contemporaneous MRI to enhance lesion detection in CaP [45]. Schettino et al. performed 58 capromab scans and compared the findings of the capromab only with the capromab-MR/CT fusion to determine whether greater accuracy is conferred [46]. The study revealed a significant difference in the findings of 47% of the patients (27/58). Interestingly, 46% were reclassified as negative, uncovering a high false positive rate rather than decreasing the known false negative rate. Sodee et al. suggested that with experience in over 600 cases and a detailed case report of 5 patients, this technique is likely to improve the high false negative rate, but there is scant pathology proven evidence to the contrary [47].

Using the fusion techniques, Ellis et al. have reported a sensitivity of 79% and specificity of 80% with the capromab-CT [48].

9. Clinical trials and future prospects

9.1. J591 imaging

While no formal prostate imaging studies of humanized J591 have been conducted, 2 independent phase I therapeutic trials have been completed where imaging was performed. The primary goal of these trials was to define the maximum tolerated dose of the therapeutic nuclides 90Y and 177Lu conjugated to J591. In these trials, imaging was performed to assess antibody targeting of known sites of metastases seen on conventional imaging. J591 imaging has demonstrated superior targeting compared with historical capromab pentetide controls. In the initial phase I study, 177Lu-J591 was able to target (image) all known sites of disease in all treated subjects [49]. A subsequent phase II study demonstrated 94% tumor targeting [26]. 111In-J591 imaging before 90Y-J591 treatment revealed 89% of known bony lesions and the majority (69%) of soft-tissue lesions [50]. In a few selected cases, J591 demonstrated lesions that were not apparent on the bone scan but were identified on MR or conventional imaging as the lesion progressed [51] (Fig. 2). SPECT images have confirmed both osseous and soft tissue uptake (Fig. 3).

In a recent retrospective review of the initial decade of experienced with radiolabeled J591 has revealed that it
targets 86.4% of known lesions on planar imaging [52]. As all the described work has utilized SPECT and therapeutic nuclides, the next generation of J591 imaging will require the conjugation of a PET nuclide, such as 89Zr, as exhibited in a murine model by Holland et al. [53]. Other PSMA antibodies have been conjugated with a PET nuclide as was done in Regino et al., but huJ591 currently is the lead agent as the antibody has extensive safety data in human subjects and has been de-immunized [31].

89Zr-DFO-labeled mAbs show exceptional promise as radiotracers for immunoPET of human cancers. 89Zr-DFO-J591 displays high tumor-to-background tissue contrast in immunoPET and can be used to delineate and quantify PSMA-positive CaP in vivo [53].

In patients with CaP, a positive surgical margin is
associated with an increased risk of cancer recurrence and poorer outcome, yet the margin status cannot be reliably determined during the surgery. Recently, an activatable mAb-fluorophore conjugate consisting of a huJ591 linked to an indocyanine green (ICG) derivative was used as a tracer. After binding to PSMA, an 18-fold activation was observed, permitting the specific detection of PSMA+/H11001 tumors up to 10 days after injection of a low dose (0.25 mg/kg) of the reagent [54]. This agent demonstrates a promising in vivo method to image the extent of CaP and can assist with real-time resection of extracapsular extension of tumor and positive lymph nodes.

As PSMA expression is downstream of the androgen receptor (AR), J591 has also shown potential as an imaging agent to predict changes in AR signaling after MDV3100, abiraterone, or other AR-targeted therapeutics. Relative changes in PSMA expression levels can be quantitatively measured using a human-ready imaging reagent and could serve as a biomarker of AR signaling to noninvasively evaluate AR activity in patients with CRPC. The changes are measured in vivo in human CaP xenograft models through PET imaging using $^{64}$Cu-J591 [55].

9.2. Small molecule inhibitors

In vitro biochemical studies of MIP-1072 and MIP-1095 demonstrated that they inhibit NAALADase activity in lysates from PSMA expressing tumors. Binding studies with intact PSMA-expressing cells demonstrated that both $^{123}$I-MIP-1072 and $^{125}$I-MIP-1095 exhibit saturable and competitive binding. In contrast, no binding was observed in cells that do not express PSMA. Furthermore, a time- and temperature-dependent increase in cell association of MIP-1072 and MIP-1095 indicated internalization via endocytosis. A series of high affinity radiolabeled PSMA inhibitors have been developed that localize specifically to PSMA-avid CaP in preclinical models, 2 of which were shown to detect both bone and soft tissue metastases in CaP patients. These radiopharmaceuticals, which are in clinical trials, may be valuable for patient management, including the diagnosis, staging, and potential treatment of CaP [56]. In initial phase I clinical trials in patients with histologically confirmed metastatic CaP, $^{123}$I-MIP-1072 and $^{125}$I-MIP-1095, detected both bone and soft tissue CaP metastases at 1 to 4 hours postinjection.

We have recently evaluated novel $^{99m}$Tc-labeled small molecule inhibitors of the enzymatic domain of PSMA. Preclinical studies with PSMA positive LNCaP cells and xenografts demonstrate that these compounds ($^{99m}$Tc-MIP-1404 and $^{99m}$Tc-MIP-1405) bind to PSMA with high affinity. In early phase I human studies, these molecules localized in tumors rapidly and identified a greater number of lesions than bone scans, and rapidly detected soft tissue CaP lesions, including sub-cm lymph nodes [57]. Given the apparent high sensitivity of these agents, future work is planned in patients with high risk localized
CaP to more accurately assess the sensitivity/specificity of this agent for occult disease.

10. Conclusions

Imaging is an emerging component of diagnostic and therapeutic management of CaP. While advances in conventional imaging will continue, Ab and small molecule imaging exemplified by PSMA targeting have the greatest potential to improve diagnostic sensitivity and specificity. To date, the most successful targeted CaP imaging is demonstrated with PSMA.

$^{111}$In-capromab remains the only Food and Drug Administration (FDA)-approved imaging agent for CaP imaging, but indirect evidence demonstrates clear inferiority to the multiple investigational PSMA-targeted agents. Its inability to image bone lesions, which is a common and early site of metastatic spread, is hindrance to clinical metrics and the agent’s future development.

Early experience with a mAb to the extracellular domain of PSMA confirms that an Ab to an extracellular epitope will have superior in vivo detection of tumor although there are no data available to compare these entities. Ultimately, a direct comparison of $^{111}$In-capromab and $^{111}$In-huJ591 on the same patients contemporaneously will be required to establish the superiority of the agent. Ideally, the next step will be a direct comparison of $^{111}$In-huJ591 and $^{89}$Zr-J591 to determine whether immunoPET confers greater lesion detection and ultimately gives quantitative information about tumor targeting, which has been indirect to date. When whole Ab imaging is optimized in human subjects, the questions in the future will likely include a comparison between whole abs and small molecule agents, which is more practical for clinical use, has better imaging characteristics, and is
better suited to guide therapeutic options. In a similar time frame, nonspecific investigational agents may have been FDA-approved or at least deemed worthy of regular use in CaP patients and some of the MRI-based or optical imaging tracers, such as quantum dots.

References


