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doi.org/10.58931/cot.2024.1326

Prostate-specific Membrane Antigen (PSMA): A Diagnostic and Therapeutic Target in Advanced Prostate Cancer

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Introduction

Prostate cancer is among the most prevalent malignant conditions globally, and both incidence and mortality are expected to increase markedly over the next two decades.[1] Recently, the diagnostic and treatment landscape for managing this disease underwent remarkable advances that led to the incorporation of innovative approaches, such as prostate-specific membrane antigen (PSMA) theranostics.[2]

PSMA, which is also known as folate hydroxylase or glutamate carboxypeptidase, is a transmembrane protein 100- to 1000-fold overexpressed by prostate cancer cells compared to healthy cells found in the benign prostate gland, salivary glands, proximal renal tubules, small intestine mucosa, and hepatocytes, amongst others.[3]

Since its discovery over 30 years ago (see **Figure 1** for this and other milestones), PSMA has caught the attention of the scientific community as a potential therapeutic target, and for the past two decades many efforts have been undertaken to identify and develop PSMA ligands and antibodies that could be exploited as prostate cancer therapeutics.[4]

This review aims to provide an overview of available PSMA ligands, their mechanisms of action, diagnostic and therapeutic applications, and future perspectives of PSMA-targeted therapeutic approaches within the field of radioligand therapy (RLT).

Mechanism of Action and Biology of PSMA Ligands

Isolated in 1993, the PSMA molecule is a 100 kDa protein encoded by the *FOLH1* gene on chromosome 11p11-12.[5] PSMA demonstrates resemblance with the transferrin receptor. Several mechanisms regulating its expression have been described to date, including co-expression/upregulation with the androgen receptor (AR) and modulation via epigenetic mechanisms. A proximal promoter and an enhancer site in the third intron are two important gene regulatory elements that have been described. Moreover, several transcription factors other than the AR play an important role in regulating PSMA expression.[5-8] Of particular interest is the relationship between PSMA expression and AR blockade, which has produced conflicting data.[9]

Structurally, the PSMA protein consists of three parts. The 707 amino acid extracellular portion contains a catalytic binding site - the enzymatic activity of which is modulated by the glycosylation of extracellular domains and by the interaction with actin-binding anchor protein filament A. Although it is hypothesized that enzymatic substrates, such as polyglutamated folate, are internalized by PSMA, specific biological ligands for PSMA remain unknown to date.[10] The mechanisms of PSMA-mediated internalization and interaction with the endosomal compartment are relevant because they are an important aspect of how small molecules and peptides bound to PSMA can exert their anticancer properties.[10]

The exact biological functions of PSMA remain to be elucidated. Besides being a tumour marker and an imaging target, the metabolites generated by its glutamate carboxypeptidase and N-acetylated a-linked acidic dipeptidase activities (i.e. folate and glutamate or N-acetyl-aspartate, respectively) are thought to be related to multiple cellular processes, such as cell growth, activation of signaling pathways, and DNA repair, which, in

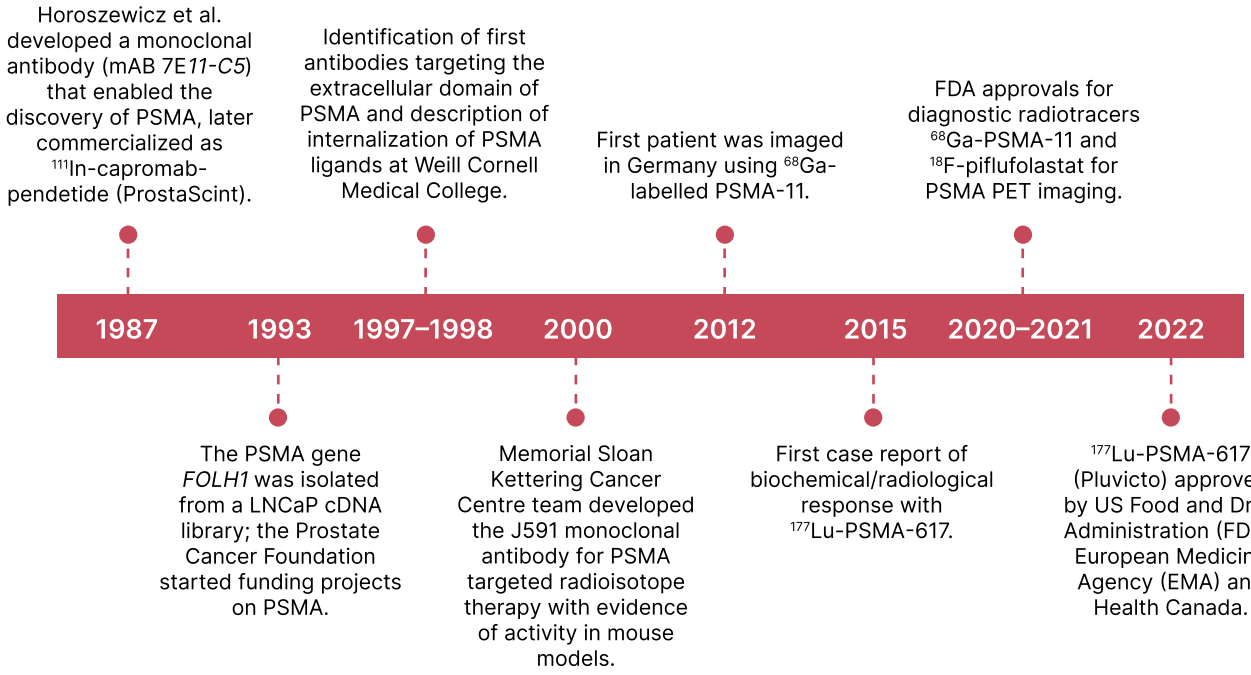

Figure 1. Timeline with key milestones in the development of PSMA theranostics[4,10]; *courtesy of Urban Emmenegger, MD and Rubens Sperandio, MD*

turn, play a role in the proliferation and survival of malignant clones. Moreover, tumoural invasiveness is also being attributed to PSMA activity, as well as contributions to neoangiogenesis in prostate and other cancers.[10]

Importantly, PSMA expression varies across clinical prostate cancer stages. The expression is higher in advanced disease settings, such as metastatic castration-resistant prostate cancer (mCRPC), and in patients with DNA damage repair gene alterations, correlating with poor prognosis and reduced survival. On the contrary, PSMA expression is suppressed in neuroendocrine prostate cancer. Moreover, it is heterogeneously expressed in metastatic sites; for instance, liver metastases tend to express lower levels of PSMA.[11]

In the past decades, PSMA has been a target of interest for diverse therapeutic approaches, including RLT, chimeric antigen receptor (CAR) T-cells, antibody-drug conjugates, and bispecific antibodies and T-cell engagers.

PSMA Diagnostics: How and When to Use

The landscape of PSMA ligands as molecular imaging tools in the diagnostic space is still evolving. The primary techniques utilizing PSMA-binding radiotracers are positron emission tomography (PET) – paired with either computed tomography (CT) or magnetic resonance imaging (MRI) – and single-photon emission computed tomography (SPECT). The use of PSMA PET scans is more widespread than SPECT, and the two agents used mostly are ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (^{18}F-piflufolastat). These tracers are very sensitive and precise in delineating the location of primary tumours, locoregional nodal involvement, and the extent and location of distant metastases in patients with prostate cancer.

PSMA PET imaging has demonstrated higher sensitivity and specificity than conventional cross-sectional imaging (using CT or MRI) and isotope bone scans. While there are differences in the isotope half-lives and practical logistics between each of the PSMA radiotracers, expert panels consider all the approved agents – ^{68}Ga-PSMA-11, ^{18}F-piflufolastat and ^{18}F-rh-PSMA-7.3 (also known as ^{18}F-flotufolastat) – to feature largely equivalent diagnostic characteristics.[12]

There is an ongoing debate in the scientific community regarding replacing conventional with molecular imaging methods, with varying degrees of evidence across the three scenarios described hereafter:

1. *Initial staging:* molecular imaging can guide the feasibility and clinical utility of local therapies, such as radiotherapy or surgical procedures.[13]

2. *Biochemical recurrence:* numerous Phase 3 trials, such as the CONDOR[14] and UCLA/UCSF[15] trials, demonstrated that PSMA-PET imaging is superior to conventional imaging and leads to changes in management in over 60% of cases.[15] Ongoing trials assess whether molecular imaging translates to superior overall survival (OS) and progression-free survival (PFS).
3. *Metastatic setting:* the clinical utility of molecular imaging in the metastatic disease setting (as documented by conventional imaging) is still debatable. Most pivotal clinical trials assessing life-prolonging therapies used conventional imaging for treatment guidance. For this reason, it remains unclear if intensifying treatment for more extensive disease that is only visible by PSMA PET imaging might result in long-term clinical benefit. Moreover, the role of PSMA PET imaging for assessing therapeutic responses is still being determined, with the potential caveat that PSMA is a cell surface antigen and not a biomarker of metabolic activity, as traditionally seen with ^{18}F-fludeoxyglucose (FDG) radiotracers.

Despite its well-documented promise, limited PSMA radiotracer availability/access and costs are barriers and may pose challenges for the widespread incorporation of PSMA diagnostic techniques in many jurisdictions, especially in remote and rural areas. Systems such as PSMA-RADS[16] and PROMISE[17] have been developed and validated with the goal of standardizing the reporting of molecular imaging findings, yet the full implementation of those tools warrants further efforts.

Therapeutic Applications: Impact of PSMA Therapies

Beyond its role in staging and treatment planning, PSMA-targeting has been explored as a vehicle for delivering potent anticancer therapies, notably in more advanced disease settings. RLT has quickly become the forerunner of this approach, by using PSMA's overexpression as a gateway to target radiotherapy to tumoural clusters. Naturally, for this approach to be effective, patients must be selected based on PSMA positivity criteria, and in this respect, trials have varied in the eligibility criteria applied **(Table 1)**. PSMA-negative lesions are commonly defined as metastatic disease with no PSMA uptake in bone lesions with a soft tissue component of ≥1 cm, lymph nodes ≥2.5 cm in the short axis, and visceral metastases of ≥1 cm in size.[18] Intra- and inter-metastatic heterogeneity of PSMA expression, which may also vary over time, is posed as a contributor to resistance to PSMA RLT.

^{177}Lu-PSMA-617 is the most developed PSMA RLT at the moment. This beta-emitting PSMA-radioligand has been approved for use in patients with mCRPC after AR pathway inhibitor (ARPI) and taxane therapy in many countries. It delivers radiation to both PSMA-expressing cells and the surrounding microenvironment within a 0.62 mm range, with a radionuclide half-life of 6.6 days.[19] The radiation effects lead to single-strand DNA breaks, resulting in eventual cell death. Several early-phase trials showed activity and promising response rates in patients with advanced prostate cancer. Given the relatively long half-life of ^{177}Lu, appropriate radiation safety precautions are recommended to minimize exposure to nuclear medicine personnel, family members, and the public. There is emerging evidence that the degree of PSMA expression may correlate with treatment response. **Table 1** summarizes nuances and differences of seminal PSMA-targeted RLT trials, including the TheraP[20], VISION[21], PSMAfore[22], and SPLASH trials.

TheraP is a randomized Phase 2 trial conducted in 11 Australian centres, involving 200 heavily pretreated patients with mCRPC post-docetaxel, randomized 1:1 between ^{177}Lu-PSMA-617 and cabazitaxel. This trial showed a greater prostate-specific antigen (PSA) response of ^{177}Lu-PSMA-617 with radiological PFS (rPFS) benefit with a hazard ratio of 0.63 (95% confidence interval [CI]: 0.46-0.86, p = 0.0028).

VISION is a multicentre, international phase 3 trial that enrolled patients with mCRPC who were pretreated with at least one line of ARPI and one line of taxane chemotherapy. It randomized patients with PSMA-positive lesions in a 2:1 fashion to standard-of-care therapy with or without ^{177}Lu-PSMA-617. The primary endpoint, median rPFS, was longer in the intervention arm, at 8.7 months, compared to 3.4 months in the standard of care arm, with a hazard ratio of 0.40 (95% CI: 0.29-0.75, p < 0.001). Median OS was an alternate primary endpoint, which was also longer for the intervention arm (15.3 vs.11.3 months) with a hazard ratio of 0.62 (95% CI: 0.52-0.74, p < 0.001).

Overall, treatment with ^{177}Lu-PSMA-617 is associated with improved OS, PFS, and quality of life measures, whereas side effects related to

Trial	TheraP	VISION	PSMAfore	SPLASH
NCT Identifier	NCT03392428	NCT03511664	NCT04689828	NCT04647526
Sample size (n)	200	831	468	412
Phase	2	3	3	3
Comparator	Cabazitaxel	Standard-of-care therapy alone (excluded Ra233, chemotherapy, immunotherapy, and other investigational agents)	ARPI change	ARPI change
Randomization	1 to 1	2 to 1	1 to 1	2 to 1
Scenario (ie, prior therapies)	post ARPI and chemotherapy	post ARPI and 1-2 lines of taxane chemotherapy	post one ARPI, chemotherapy-naïve (except [neo]adjuvant ≥ 12 months ago)	post one ARPI, not eligible for or refusing chemotherapy
Selection criteria	^{68}Ga-PSMA-11 PET CT with SUVmax ≥20 in at least ≥1 disease site and >10 at all other metastatic disease sites, and no discordant FDG PET-positive lesions	^{68}Ga-PSMA-11 PET CT with lesion uptake greater than liver parenchyma at ≥1 disease site(s) and no PSMA-negative metastatic lesions	^{68}Ga-PSMA-11 with lesion uptake greater than liver parenchyma at ≥1 disease site and no PSMA-negative metastatic lesions	PSMA-PET scan (i.e., ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL) positive disease as determined by the sponsor's central reader
Dosing	^{177}Lu-PSMA-617: 8.5 GBq initially, reduced by 0.5 GBq per cycle, q6w, up to 6 cycles	^{177}Lu-PSMA-617: 7.5GBq q6w x 4-6 cycles (extended if evidence of response and residual disease) + standard of care therapy	7.4 GBq ± 10% q6w x 6 cycles	^{177}Lu-PNT2002: 6.8 GBq ± 10% q8w x 4 cycles
Primary endpoint(s)	PSA response rate	rPFS, OS (alternate)	rPFS by BICR	rPFS by BICR
PSA50	66%	46%	57.6%	N/A
ORR RECIST	49%	51%	50.7%	N/A

Trial	TheraP	VISION	PSMAfore	SPLASH
Median rPFS	5.1. months versus 5.1 months (HR 0.63, 95% CI 0.46-0.86, p=0.0028)	8.7 months versus 3.4 months (HR 0.40, 95% CI 0.29-0.57, p<0.001)	12.02 months versus 5.59 months (HR 0.41, 95% CI 0.29-0.56, p<0.0001)	9.5 months versus 6.0 months (HR 0.71; p=0.0088)
Median OS	19.1 months vs 19.6 months (restricted mean survival time; p=0·77)	15.3 months versus 11.3 months (HR 0.62, 95% CI 0.52-0.74, p<0.001)	23.66 months versus 23.85 months (HR 0.98, 95% CI 0.79-1.27, p=N/A)	N/A (HR 1.11)
Comments			84.2% crossover rate	84% crossover rate

Table 1. Seminal PSMA-targeted radioligand therapy trials; *courtesy of Urban Emmenegger, MD and Rubens Sperandio, MD*

Abbreviations: ARPI: androgen receptor pathway inhibitor; **BICR:** blinded independent central review; **CI:** confidence interval; **CT:** computed tomography; **FDG:** ^{18}F-fludeoxyglucose; **HR:** hazard ratio; **N/A:** not available; **ORR:** overall response rate; **OS:** overall survival; **PET:** positron emission tomography; **PSA:** prostate-specific antigen; PSA50: 50% or higher PSA response; **PSMA:** prostate-specific membrane antigen; **RECIST:** Response Evaluation Criteria in Solid Tumours**; RLT:** radioligand therapy; **rPFS:** radiological progression-free survival; **SUV:** standardized uptake value.

^{177}Lu-PSMA-617 are typically mild and manageable. Side effects include myelosuppression, gastrointestinal symptoms, such as nausea, xerostomia due to the expression of PSMA in salivary glands, and deteriorating renal function. The current development of PSMA RLT involves the study of such agents in earlier disease stages, such as chemotherapy-naïve mCRPC (PSMAfore, SPLASH) and metastatic castration-sensitive prostate cancer (PSMAddition).

Future of PSMA-targeted Therapies

The use of PSMA RLT does not come without challenges, including limited access or lack of public funding to date in many jurisdictions. Furthermore, inherent therapeutic resistance is not uncommon, and acquired resistance is the typical ultimate outcome. Hence, diverse strategies are exploring ways of improving patient outcomes.[23] Radioligands are being refined in order to improve affinity and decrease toxicity. Using radionuclides other than ^{177}Lu, such as the alpha emitter ^{225}Ac, has shown promising results in retrospective studies, including in ^{177}Lu-resistant cases. Combination strategies to overcome therapeutic resistance are being evaluated in many clinical trials testing poly (ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, and the concurrent use of ARPI amongst others.

Conclusion

In conclusion, PSMA theranostics represent a paradigm shift in the management of prostate cancer, offering both diagnostic precision and therapeutic efficacy. As we continue to unravel the full potential of PSMA-targeted approaches, the future holds great promise for further advancements toward personalized prostate cancer care.

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Financial Disclosures:

U.E.: Paid consulting activities for AAA/Novartis; financial support for conducting several clinical trials involving radioligands (to the Sunnybrook Research Institute).
R.C.S.: None declared.

References:

1. James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, et al. The Lancet Commission on prostate cancer: planning for the surge in cases. Lancet. 2024;S0140673624006512.
2. Tilki D, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Part II-2024 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2024;S0302-2838(24)02306-6.
3. Kinoshita Y, Kuratsukuri K, Landas S, Imaida K, Rovito PM, Wang CY, et al. Expression of prostate-specific membrane antigen in normal and malignant human tissues. World J Surg. 2006;30(4):628–36.
4. Mattana F, Muraglia L, Barone A, Colandrea M, Saker Diffalah Y, Provera S, et al. Prostate-Specific Membrane Antigen-Targeted Therapy in Prostate Cancer: History, Combination Therapies, Trials, and Future Perspective. Cancers. 2024;16(9):1643.
5. O'Keefe DS, Su SL, Bacich DJ, Horiguchi Y, Luo Y, Powell CT, et al. Mapping, genomic organization and promoter analysis of the human prostate-specific membrane antigen gene. Biochim Biophys Acta. 1998;1443(1–2):113–27.
6. Watt F, Martorana A, Brookes DE, Ho T, Kingsley E, O'Keefe DS, et al. A tissue-specific enhancer of the prostate-specific membrane antigen gene, FOLH1. Genomics. 2001;73(3):243–54.
7. Peng W, Guo L, Tang R, Liu X, Jin R, Dong JT, et al. Sox7 negatively regulates prostate-specific membrane antigen (PSMA) expression through PSMA-enhancer. The Prostate. 2019;79(4):370–8.
8. Yin L, Rao P, Elson P, Wang J, Ittmann M, Heston WDW. Role of TMPRSS2-ERG gene fusion in negative regulation of PSMA expression. PloS One. 2011;6(6):e21319.
9. Emmett L, Yin C, Crumbaker M, Hruby G, Kneebone A, Epstein R, et al. Rapid Modulation of PSMA Expression by Androgen Deprivation: Serial 68Ga-PSMA-11 PET in Men with Hormone-Sensitive and Castrate-Resistant Prostate Cancer Commencing Androgen Blockade. J Nucl Med Off Publ Soc Nucl Med. 2019;60(7):950–4.
10. Denmeade SR. Resolute Progress Down a Long and Winding Road Leads to the Promised Land of Prostate-Specific Membrane Antigen–Based Therapies for Prostate Cancer. J Clin Oncol. 2024;42(7):852–6.
11. Wright GL, Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol. 1995;1(1):18–28.
12. Schaeffer EM, Srinivas S, Adra N, An Y, Bitting R, Chapin B, et al. Prostate Cancer, Version 3.2024. J Natl Compr Cancer Netw JNCCN. 2024;22(3):140–50.
13. Bennett R, Li E, Ho AY, Aguiar J, Mahenthiran AK, Kumar S, et al. Patterns of PSMA PET/CT scan usage for initial staging and recurrence in a multi-centered hospital system. J Clin Oncol. 2024;42(4_suppl):36–36.
14. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, et al. Diagnostic Performance of 18F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res Off J Am Assoc Cancer Res. 2021;27(13):3674–82.
15. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncol. 2019;5(6):856–63.
16. Seifert R, Emmett L, Rowe SP, Herrmann K, Hadaschik B, Calais J, et al. Second Version of the Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation for Clinical Trials (PROMISE V2). Eur Urol. 2023;83(5):405–12.
17. Werner RA, Hartrampf PE, Fendler WP, Serfling SE, Derlin T, Higuchi T, et al. Prostate-specific Membrane Antigen Reporting and Data System Version 2.0. Eur Urol. 2023;84(5):491–502.
18. Kuo PH, Benson T, Messmann R, Groaning M. Why We Did What We Did: PSMA PET/CT Selection Criteria for the VISION Trial. J Nucl Med Off Publ Soc Nucl Med. 2022;63(6):816–8.
19. Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov. 2020;19(9):589–608.
20. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet Lond Engl. 2021;397(10276):797–804.
21. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385(12):1091–103.
22. O. Sartor, D.E. Castellano Gauna, K. Herrmann, J.S. de Bono, N.D. Shore, K.N.N. Chi, et al. LBA13 - Phase III trial of [177Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore). In: Ann Oncol. (2023) 34 (suppl_2): S1254-S1335 101016/S0923-7534(23)04149-2. Madrid, Spain; 2023.
23. Gafita A, Marcus C, Kostos L, Schuster DM, Calais J, Hofman MS. Predictors and Real-World Use of Prostate-Specific Radioligand Therapy: PSMA and Beyond. Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Annu Meet. 2022;42:1–17.