The History of Prostate-Specific Membrane Antigen as a Theranostic Target in Prostate Cancer: The Cornerstone Role of the Prostate Cancer Foundation

Andrea K. Miyahira and Howard R. Soule

Science Department, Prostate Cancer Foundation, Santa Monica, California

Prostate-specific membrane antigen (PSMA) is a credentialled imaging and therapy (theranostic) target for the detection and treatment of prostate cancer. PSMA-targeted PET imaging and molecular radiotherapy are promising evolving technologies that will improve the outcomes of prostate cancer patients. In anticipation of this new era in prostate cancer theranostics, this article will review the history of PSMA from discovery through early- and late-stage clinical trials. Since 1993, the Prostate Cancer Foundation has funded critical and foundational PSMA research that established this theranostic revolution. The history and role of Prostate Cancer Foundation funding in this field will be discussed.

Key Words: theranostics; prostate cancer; PSMA; PET imaging; molecular radiotherapy

J Nucl Med 2022; 63:331–338 DOI: 10.2967/jnumed.121.262997

The Prostate Cancer Foundation (PCF) was established in 1993 as CaP CURE, the first nonprofit global organization with a mission of funding basic, translational, and clinical research to discover better diagnostics and treatments for advanced prostate cancer. The prostate-specific membrane antigen (PSMA) represents one of the earliest and most constant research areas funded by PCF, with the first project funding given in 1994 to William Fair and Neil Bander for PSMA theranostics applications. Since its inception, PCF has funded over $28.5 million for research on PSMA biology, molecular imaging, and therapy. Many advancements in the biologic understanding and clinical applications that exploit PSMA have a foundation in PCF funding.

BIRTH: DISCOVERY AND EARLY CHARACTERIZATION

The discovery of PSMA can be first traced to Murphy and Horoszewicz’s team (1), who developed the 7E11-C5 monoclonal antibody (capromab) from mice immunized with the human prostate-cancer-derived cell line LNCaP in 1987. 7E11-C5 recognized an antigen restricted to normal and malignant prostate epithelium and present in the sera of some prostate cancer patients. Horoszewicz et al. concluded that this “new antigenic marker may be of clinical potential in [prostate cancer].”

Using 7E11-C5, Heston and Fair’s group (2,3) at Memorial Sloan Kettering Cancer Center cloned the PSMA gene in 1993. PSMA, also known as folate hydrolase 1 and glutamate carboxypeptidase II (GCP-II), is a 750-amino-acid, 100-kD, type II transmembrane protein with a short N-terminal intracellular domain and a large C-terminal extracellular domain (2). PSMA is expressed predominantly in the prostate and a subset of proximal renal tubules, with lower expression in the small bowel, salivary glands, and some glial cells in the brain (1–5). In 1993, Heston’s group (2) concluded that “as an integral membrane protein unique to prostatic epithelial cells, the antigen or perhaps a specific PSMA ligand may serve as an excellent site for imaging and/or targeting of metastatic deposits,” setting the stage for PSMA as a theranostic target.

In 1994 and 1995, Fair and Heston’s groups obtained PCF funding and described PSMA as a folate hydrolase highly expressed in prostate cancer (6), further detailed its tissue distribution (3), and mapped its genomic organization on chromosome 11p11–12 (3,7). PSMA expression was observed in most (~95%) primary prostate cancer and lymph node metastases, consistent with observed 7E11-C5 immunoreactivity (1,3,8,9). PSMA was also expressed on the neovascularure of epithelial malignancies, including renal cell, bladder, and colon cancers (5).

YOUTH: EARLY EVIDENCE OF UTILITY

Anti-PSMA Antibody Development

Development of 7E11-C5 as a theranostic agent began before identification of PSMA as its target (8,10,11). In 1996,111In-capromab pendetide (ProstaScint; EUSA Pharma) became the first U.S. Food and Drug Administration (FDA)-approved molecular imaging agent for prostate cancer. 7E11-C5 targets an intracellular epitope of PSMA (1,12), binding only dying or dead cells. This fact limited ProstaScint performance as an imaging agent, particularly in well-vascularized bone metastases.

The first antibodies to the extracellular domain of PSMA were developed in 1997 with PCF funding by Bander’s team (13) at Weill Cornell Medical College. JS91, the lead antibody, enabled studies of PSMA in viable cells. Bander’s team (14) demonstrated that PSMA is constitutively internalized and that antibody binding increased the rate of internalization by severalfold. This property, the authors noted, “should aid the development of novel therapeutic methods to target the delivery of toxins, drugs, or short-range isotopes specifically to the interior of prostate cancer cells.”

Scheinberg and team (Memorial Sloan Kettering Cancer Center) received PCF funding to develop α-particle-emitting antibody molecular radiotherapy (MRT) constructs for prostate cancer.
Bander, Scheinberg’s team (15,16) demonstrated preclinical activity for 213Bi-J591 and 225Ac-J591 conjugates. Bander’s team (17) further demonstrated promising antitumor efficacy of the β-emitting conjugates 90Y-J591 and 177Lu-J591 in preclinical models.

Humanized J591 (huJ591) was developed to increase its clinical potential (18) and advanced to prostate cancer theranostics trials.

**PSMA-Targeted Ligand Development**

In 2001, Kozikowski’s group (Georgetown University) (19) developed urea-based inhibitors of the neurotransmitter regulator GCP-II (NAALADase), a central nervous system version of PSMA, as potential neuroprotective agents. The urea-based motif (glutamate-urea-lysine) binds with high affinity to the extracellular domain of GCP-II (PSMA) (20). Pomper et al. (Johns Hopkins University) (21) recognized the potential for pivoting Kozikowski’s inhibitors to PSMA-targeting agents and that they would be amenable to radiolabeling for molecular imaging or therapy. Pomper (21,22) led the first in vivo animal studies evaluating GCP-II–targeted urea-based ligands as PET and SPECT agents. Pomper’s team (22) concluded that with these low-molecular-weight urea-based agents, “we believe that we have the rudiments of a novel and practical approach to prostate cancer imaging.” Most currently studied PSMA-targeted ligands are derivatives of these early urea-based compounds.

Pomper’s team further developed the PSMA-targeted PET imaging ligands 18F-DCFBC in 2008 (23) and 18F-DCFPyL (PyL) in 2011 (24), as well as the first 68Ga-labeled PSMA-targeted ligands in 2010 (25).

The PET tracer 68Ga-PSMA-11 (68Ga-PSMA-HBED-CC; 68Ga-DKFZ-PSMA-11) was developed by Eder et al. (German Cancer Research Center) and was reported in 2012 (26).

18F-DCFPyL and 68Ga-PSMA-11 are the most-studied PSMA-targeted PET tracers. Both have recently been FDA-approved. Clinical development of these is discussed later in this article.

Development and promising first clinical experiences with the PSMA-targeted ligand 177Lu-PSMA-DOTAGA-FFK(Sub-KuE), and its improved derivative PSMA I&T, were respectively reported by Baum’s team (Zentralklinik Bad Berka) in 2014 (27) and by Weineisen et al. (Technische Universität München) in 2015 (28).

In 2015, Eder’s team (29) and Kratochwil et al. (University Hospital Heidelberg) (30) reported development and first clinical experiences with the PSMA-targeting ligand PSMA-617. 68Ga-PSMA-617 showed promise as a PET tracer (29), and the metastatic castration-resistant prostate cancer (mCRPC) patient treated with 177Lu-PSMA-617 experienced radiologic and prostate-specific antigen (PSA) responses (30).

Additional clinically studied PSMA-targeting ligands include MIP-1095, rhPSMA-7, PSMA-1007, and PSMA-R2 (31).

**ADOLESCENCE: TRANSLATION**

**Clinical Development of PSMA PET**

Two PSMA PET imaging agents are FDA-approved for prostate cancer, 68Ga-PSMA-11 (for use at University of California, Los Angeles [UCLA] and the University of California San Francisco [UCSF]) and 18F-DCFPyL. PCF funding contributed to the development of both. We detailed the clinical development of these agents and compared them other prostate cancer imaging technologies (31).

18F-DCFpyL PET, 18F-DCFBC was the predecessor of 18F-DCFpyL. In early PCF-funded clinical studies led by Pomper and Cho (32–34), 18F-DCFBC outperformed 99mTc-methylene diphosphonate bone scans and contrast-enhanced CT in detecting prostate cancer metastases but exhibited slow blood pool clearance. This resulted in high background and diminished resolution (32,33). Compared with MRI, 18F-DCFBC PET was less sensitive for detecting primary prostate cancer but more specific for clinically significant lesions (34).

18F-DCFpyL has higher PSMA binding affinity and lower blood-pool activity than 18F-DCFBC and became the agent of choice for additional PCF-funded clinical development at Johns Hopkins. The first clinical experience with 18F-DCFpyL, reported in 2015, demonstrated safety, significant tumor-specific uptake, and expected tissue biodistribution (35). 18F-DCFpyL was superior to bone scanning and CT in a lesion-by-lesion comparative study (36). In subsequent phase 2 trials, some supported by PCF, 18F-DCFpyL showed impressive performance for initial staging and for detecting biochemical recurrence (37). In 2015, 18F-DCFpyL was licensed from Johns Hopkins by Progenics Pharmaceuticals (now Lantheus), which sponsored the FDA new-drug-application (NDA)–enabling OSPREY and CONDOR trials.

In the phase 2/3 OSPREY trial (NCT02981638), led by Pienta (Johns Hopkins University) and Morris (Memorial Sloan Kettering Cancer Center) (37), 18F-DCFpyL PET/CT demonstrated medians of 97.9% specificity and 40.3% sensitivity for detecting pelvic lesions in patients with high-risk prostate cancer undergoing radical prostatectomy with pelvic lymphadenectomy and medians of 95.8% sensitivity and 81.9% positive predictive value for detecting metastases in patients with suspected recurrent or metastatic lesions seen on conventional imaging. In the phase 3 CONDOR trial (NCT03739684), reported by Morris et al. (38), 18F-DCFpyL PET/CT correctly localized prostate cancer metastases in approximately 85% of patients with biochemical recurrence, on the basis of a comparison with a composite standard of truth, and changed planned management in 64% of patients. Results from OSPREY and CONDOR led to FDA approval for 18F-DCFpyL PET (Pylarify; Lantheus) in May 2021 for imaging patients with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy and patients with suspected recurrence based on an elevated serum PSA level (39).

68Ga-PSMA-11 PET. 68Ga-PSMA-11 is the most widely used PSMA PET imaging agent internationally, since it can be produced by any facility able to perform 68Ga labeling.

The first clinical PET/CT imaging experience with 68Ga-PSMA-11 was reported in 2012 by Zechmann’s group (University Hospital Heidelberg) (40). Metaanalyses of 68Ga-PSMA-11 PET from 4,790 patients across 37 publications estimated a detection rate of 95%,

---

**NOTEWORTHY**

- PSMA is the most credentialed target for prostate cancer imaging and therapy.
- PSMA PET is a highly sensitive and specific prostate cancer imaging technology, with 2 FDA-approved agents to date.
- The phase 3 VISION trial demonstrated life-prolonging efficacy of PSMA-targeted MRT and is anticipated to lead to FDA approval.
- Since 1994, PCF has funded many foundational advancements in PSMA biology and clinical applications.
75%, 59%, 45%, and 33% for PSA levels of 2 ng/mL or more and 1–1.99, 0.5–0.99, 0.2–0.49, and 0–0.19 ng/mL, respectively (41).

In 2016, Hofman and Murphy’s group (Peter MacCallum Cancer Centre, Australia) (42) initiated the first randomized study of 68Ga-PSMA-11 PET (ProPSMA study). This 10-center, 300-patient, phase 3 study demonstrated a 27% absolute improved accuracy of PSMA PET compared with CT/bone scans.

A PCF-funded UCLA–UCSF team led by Hope, Czernin, Calais, and Fendler (43,44) conducted 2 prospective NDA-enabling trials for 68Ga-PSMA-11 PET. In patients with biochemical recurrence (NCT02940262 and NCT03335740), lesion detection rates with 68Ga-PSMA-11 PET were 97%, 86%, 84%, 57%, and 38% for PSA levels of at least 5.0 ng/mL and 2.0–5.0, 1.0–2.0, 0.5–1.0, and less than 0.5 ng/mL, respectively. The positive predictive value was 92% by composite validation assessment (43). A phase 3 study (NCT03368547) investigating 68Ga-PSMA-11 in presurgical patients with intermediate- to high-risk prostate cancer reported 40% sensitivity and 95% specificity for detection of pelvic nodal metastases (44). This team also found 68Ga-PSMA-11 to be superior to 18F-fluciclovine PET/CT in patients with biochemical recurrence at low PSA levels (<2.0 ng/mL) in a prospective comparison (NCT03515577) (45). In December 2020, 68Ga-PSMA-11 became the first FDA-approved PSMA PET agent, for use at UCLA and UCSF, for initial staging in prostate cancer patients with suspected metastasis who are candidates for initial definitive therapy and patients with suspected recurrence based on elevated PSA levels (46,47). This label allows other organizations able to produce 68Ga-PSMA-11 to file an abbreviated NDA (46). The entirely academic development of 68Ga-PSMA-11 is a noteworthy achievement, and PCF was proud to have funded the UCLA–UCSF team.

Ongoing Investigations on PSMA PET

Ongoing trials are evaluating the role for PSMA PET in other prostate cancer settings, including radiotherapy planning for localized or oligometastatic disease, and in the initial diagnosis of prostate cancer. For example, the PCF-funded ORIOLE trial led by Tran (Johns Hopkins University) tested the use of stereotactic body radiation therapy in oligometastatic prostate cancer based on conventional imaging scans. A post hoc analysis of ORIOLE found that progression-free survival and distant metastasis-free survival were significantly longer in patients who received consolidation of all PSMA PET–detectable disease, suggesting a role for PSMA PET in guiding stereotactic body radiation therapy planning in patients with oligometastatic prostate cancer (48). Additionally, PSMA PET is being investigated as a biomarker for selecting patients for PSMA-directed therapy, including 177Lu-PSMA-617.

Several other PSMA PET agents are under development. These include 18F-PSMA-1007 and 18F-rhPSMA, which have entered phase 3 trials.

Standardizing PSMA PET Imaging Reporting and Use

Structured reporting systems have been developed to standardize the clinical use and reporting of 18F- and 68Ga-based PSMA PET imaging. These include PSMA-RADS, developed with PCF support by the team of Rowe (Johns Hopkins University) and Pomper (49); PSMA-RADS is now included in the umbrella Molecular Imaging Reporting and Data Systems.

Limitations of PSMA PET have previously been detailed (53) and include loss of PSA expression in some patients with advanced castration-resistant prostate cancer or neuroendocrine prostate cancer, heterogeneity in PSMA expression, and resolution limits.

PSMA PET as an Imaging Agent in Other Cancers

Because of expression of PSMA on tumor vasculature, PSMA PET may have potential for imaging other cancer types. In a PCF-funded study on 5 patients with metastatic renal cell carcinoma, 18F-DCFPyL PET/CT exhibited a sensitivity of 94.7% and identified more putative metastatic lesions than did conventional imaging (50). An ongoing trial is further testing 18F-DCFPyL PET/CT in renal cell carcinoma (NCT02687139).

Clinical Development of PSMA-Targeted MRT

The first PSMA-targeted radionuclide tested as a therapeutic agent in prostate cancer patients was 7E11-C5.3 (90Y-capromab pendetide) (51). However, significant bone marrow toxicity and no objective clinical responses were observed in phase 1 and 2 trials (51,52).

Beginning in 2000, Bander and Nanus’ team (53,54) and Tagawa et al. (55) (Weill Cornell Medical College) initiated a series of phase 1 and 2 trials testing hu591-based MRT in advanced prostate cancer, several of which were PCF-supported. These studies represented the first clinical use of 177Lu as a systemically administered agent and demonstrated safety, accurate targeting of metastatic prostate cancer sites, and preliminary antitumor activity for 90Y-hu591 and 177Lu-hu591, providing the first direct clinical evidence supporting the potential of PSMA-targeted MRT (53–55).

Bander’s team (56) also demonstrated safety, feasibility, and promising activity with dose-fractionated 177Lu-hu591, with higher cumulative doses associated with longer median overall survival and increased myelosuppression. In another PCF-funded trial, fractionated 177Lu-hu591 administered concurrently with standard docetaxel was tolerable and feasible, with no dose-limiting toxicities observed and preliminary efficacy indicated (57). To date, this is the only trial testing PSMA MRT in combination with chemotherapy.

The first PSMA-targeted small molecule-based MRTs tested in patients included 177Lu-PSMA-DOTAGA-FFK(Sub-KuE) and 181-I-MIP-1095; antitumor activity for both was reported in 2014 (27,58).

Clinical Development of 177Lu-PSMA-617

After their 2015 report on an individual patient treated with 177Lu-PSMA-617 (30), in 2016 Kratochwil et al. reported on 30 patients with PSMA PET–positive mCRPC treated with 1–3 cycles of 177Lu-PSMA-617. Forty-three percent experienced a PSA reduction of at least 50% (39). In a multicenter retrospective report evaluating 145 patients treated at German centers, PSA declines of at least 50% were observed in 45% of 99 patients with follow-up data (60).

The first prospective trial testing 177Lu-PSMA-617 was led by Hofman (61,62) at the Peter MacCallum Cancer Centre in Australia (LuPSMA trial; ACTRN12615000912583). This single-arm phase 2 trial enrolled 50 PSMA PET–positive mCRPC patients for whom conventional therapies had failed. Patients with PSMA-negative/18F-FDG PET–positive lesions were excluded. Patients received up to 4 doses of 177Lu-PSMA-617 (mean radioactivity, 7.5 GBq) approximately every 6 wk. Sixty-four percent of patients experienced PSA reductions of at least 50% (61,62). Quality-of-life measures, including pain severity, were improved. Unfortunately, all 50 patients eventually experienced disease progression. The trial results led to the acquisition of PSMA-617 by Endocyte (now Novartis) from ABX GmbH, an acquisition that accelerated clinical development, including the phase 3 VISION trial (63).
A PCF-supported randomized phase 2 trial led by Czernin and Calais (64) at UCLA tested up to 4 cycles of 6.0 versus 7.4 GBq of \(^{177}\text{Lu-PSMA-617}\) every 8 wk in PSMA PET–positive mCRPC (RESIST-PC; NCT03042312). No significant differences were observed between the treatment arms. Of 43 patients in the UCLA cohort, 37% experienced PSA reductions of at least 50%, and the median overall survival was 14.0 mo.

A PCF-supported phase 1/2 trial led by Bander and Tagawa (65) tested dose-fractionated \(^{177}\text{Lu-PSMA-617}\) in unsel ected mCRPC patients (NCT03042468). No maximum tolerable dose or dose-limiting toxicities were observed with 1 cycle of fractionated cumulative doses of 7.4–22 GBq. Of 44 patients treated, 59.1% had a PSA decline of more than 50%, and the median overall survival was 16 mo. Of note, this is the only conventional dose-escalation trial done for \(^{177}\text{Lu-PSMA-617}\).

### ADULT: THERANOSTICS REVOLUTION

The phase 2 Therap trial (NCT03392428; ANZUP 1603), reported by Hofman et al. (66), was the first randomized trial comparing \(^{177}\text{Lu-PSMA-617}\) with a standard treatment in mCRPC, cabazitaxel. This trial enrolled 200 patients with PSMA PET–positive mCRPC and no PSMA-negative/\(^{18}\text{F-FDG PET–positive lesions (of 291 screened by PET [69%]) who had previously experienced disease progression on docetaxel (91% had prior abiraterone or enzalutamide). The primary endpoint, a PSA decline of at least 50%, was experienced by significantly more patients treated with \(^{177}\text{Lu-PSMA-617}\) (66%) than patients treated with cabazitaxel (44%). Analysis of secondary endpoints is ongoing. Grade 3–4 treatment-emergent adverse events were lower among patients treated with \(^{177}\text{Lu-PSMA-617}\) (33%) than among patients treated with cabazitaxel (53%).

The Novartis/Endocyte-sponsored international randomized open-label phase 3 VISION trial (NCT03511664), testing \(^{177}\text{Lu-PSMA-617}\) plus protocol-permitted standard of care (SOC; excluding chemotherapy, immunotherapy, \(^{223}\text{Ra}, and investigational drugs) versus SOC alone (randomized 2:1), was initiated in 2018, led by Morris and Sarto (Tulane University) (67). The trial enrolled 831 patients with PSMA PET–positive mCRPC whose disease had previously progressed on docetaxel and an antiandrogen therapy. \(^{177}\text{Lu-PSMA-617}\) dosing consisted of 7.4 GBq every 6 wk for 4–6 cycles. The trial initially suffered from significant control-arm attrition, which was reduced on implementation of enhanced trial-site education. The radiographic progression-free survival analysis included only patients enrolled after education measures had been implemented \((n = 581\)), whereas the overall survival analysis included all 831 patients. The addition of \(^{177}\text{Lu-PSMA-617}\) to SOC significantly prolonged both alternate primary endpoints: median overall survival (15.3 vs. 11.3 mo; hazard ratio, 0.62) and median radiographic progression-free survival (8.7 vs. 3.4 mo; hazard ratio, 0.40). All key secondary endpoints significantly favored \(^{177}\text{Lu-PSMA-617}\), including time to first symptomatic skeletal event (median, 11.5 vs. 6.8 mo), objective response rate (29.8% vs. 1.7%), and disease control rate (89.0% vs. 66.7%). Complete responses occurred in 9.2% of patients with measurable disease in the \(^{177}\text{Lu-PSMA-617}\) arm versus none in the control arm, and partial responses occurred in 41.8% of patients in the \(^{177}\text{Lu-PSMA-617}\) arm versus 3% in the control arm. Although a higher rate of adverse events of grade 3 or higher were observed with \(^{177}\text{Lu-PSMA-617}\) (52.7% vs. 38.0%), health-related quality-of-life scores were improved. The most common treatment-emergent adverse events in the \(^{177}\text{Lu-PSMA-617}\) group were fatigue, dry mouth, and nausea, with the vast majority being a grade 1 or 2 event (39% experienced grade 1–2 dry mouth, with no events of grade or higher). Five grade 5 drug-related deaths occurred in the \(^{177}\text{Lu-PSMA-617}\) arm. On the basis of these data, \(^{177}\text{Lu-PSMA-617}\) was granted breakthrough-therapy designation and priority review by the FDA in 2021.

Two additional phase 3 trials have been initiated to test \(^{177}\text{Lu-PSMA-617}\) in earlier disease settings. PSMAfore (NCT04689828) is testing \(^{177}\text{Lu-PSMA-617}\) versus a change in androgen receptor (AR)–targeted therapy in taxane-naïve mCRPC patients whose disease previously progressed on an alternate AR-targeted therapy. PSMAdition (NCT04720157) is testing \(^{177}\text{Lu-PSMA-617}\) plus SOC (AR-targeted therapy plus androgen deprivation therapy) versus SOC alone in patients with metastatic hormone-sensitive prostate cancer. The primary endpoint for both studies is radiographic progression-free survival.

Other trials testing \(^{177}\text{Lu-PSMA-617}\) in earlier settings are ongoing. For instance, UpFrontPSMA (NCT04343885), led by Azad and Hofman, is a randomized phase 2 trial comparing \(^{177}\text{Lu-PSMA-617}\) plus androgen deprivation therapy followed by docetaxel versus androgen deprivation therapy plus docetaxel in patients with de novo metastatic prostate cancer. LuTectomy (NCT04430192) is a phase 1/2 trial testing neoadjuvant \(^{177}\text{Lu-PSMA-617}\) in patients with high-risk localized or locoregional advanced prostate cancer undergoing radical prostatectomy and pelvic lymph node dissection.

### Other β-Emitting PSMA MRTs Under Development

In addition to \(^{177}\text{Lu-PSMA-617}\) and \(^{177}\text{Lu-hu591}\), several other \(\beta\)-emitting PSMA-targeted MRTs are under development. These include \(^{177}\text{Lu-PSMA-I&T (PNT2002; POINT Biopharma), which is being tested in the phase 3 SPLASH trial in patients with PSMA PET–positive mCRPC whose disease has progressed on AR-targeted therapy (NCT04647526). This 2-part study consists of a safety and dosimetry lead-in, followed by a randomization phase comparing \(^{177}\text{Lu-PSMA-I&T versus abiraterone or enzalutamide. \(^{177}\text{Lu-DOTA-rosopatamab (TLX591; Telix Pharmaceuticals) is a PSMA-targeted antibody-based MRT that is being tested in the phase 3 ProstACT trial (NCT04876651) in combination with SOC versus SOC alone, in patients with PSMA PET–positive mCRPC who have experienced disease progression on AR-targeted therapy.}

### Clinical Development of α-Emitting PSMA MRTs

\(\alpha\)-emitting radioisotopes emit a much higher energy over a shorter distance, and are more effective inducers of double-stranded DNA breaks, than \(\beta\)-emitting radioisotopes. \(\alpha\)-emitting PSMA-targeted MRT agents are being studied for prostate cancer. \(^{225}\text{Ac-PSMA-617}\). In 2016, Kratochwil, Morgenstem (Institute for Transuranium Elements) and team (68) reported on 2 mCRPC patients treated with \(^{225}\text{Ac-PSMA-617}\) who experienced complete PSA and imaging responses. Moderate to severe xerostomia was the only treatment-emergent adverse event reported. In 2018 (69), the group published on 40 consecutive mCRPC patients treated with up to 3 cycles of \(^{225}\text{Ac-PSMA-617}\). Of 38 patients who survived over 8 wk, 63% experienced PSA declines of at least 50%. Five patients had enduring responses lasting over 2 y.

Promising anecdotal clinical experiences with \(^{225}\text{Ac-PSMA-617}\) have also been reported by groups in Germany, India, and South Africa. The first planned clinical trials with \(^{225}\text{Ac-PSMA-617}\)
include a pilot trial in China (NCT04225910) and a phase 1 study in Australia and South Africa (NCT04597411).

Strategies are needed to prevent xerostomia and other adverse late effects of $^{225}$Ac-PSMA-617. $^{225}$AC-HUJ591. Because of the larger molecular mass of J591 and lack of detectable uptake in the salivary and lacrimal glands (70), Bander, Tagawa, and team hypothesize that $^{225}$Ac-huJ591 could deliver promising antitumor activity without xerostomia. The team received PCF funding to support clinical testing of $^{225}$Ac-huJ591. In a single ascending dose phase 1 trial in (71) 32 mCRPC patients unselected by PSMA PET (NCT03276572), $^{225}$Ac-huJ591 was well tolerated, with no maximum tolerable dose reached. 68.8% of patients experienced any PSA decline, and 43.8% experienced at least a 50% PSA decline. A follow-up phase 1/2 dose escalation trial is testing fractionated and multiple dosing regimens of $^{225}$Ac-huJ591 (NCT04506567). As J591 binds a PSMA site different from that bound by the urea-based ligands, and the normal tissue biodistributions have little overlap, Bander has proposed that combining these agents may increase dose to tumor without increasing toxicity. A trial testing $^{225}$Ac-huJ591 in combination with $^{177}$Lu-PSMA-I&T began in 2021 (NCT04886986).

Other $\alpha$-Emitting MRT Agents in Development

Other $\alpha$-emitting MRTs in development include the $^{227}$Th-labeled anti-PSMA antibody $^{227}$Th-PSMA-TTC (BAY 2315497; Bayer), which is in a phase I study in mCRPC (NCT 03724747). $^{213}$Bi-PSMA-617 is also being studied in mCRPC.

Agents in preclinical development include $^{225}$Ac-RPS-074, an albumin-binding PSMA-targeted ligand with an extended serum half-life developed by Babich’s team (Weill Cornell Medicine) (72), and CA012, a novel PSMA-targeted ligand developed in Heidelberg, which can be radiolabeled with lead-based radioisotopes, such as the $\alpha$-emitter $^{212}$Pb (73).

Rational Therapeutic Combinations with PSMA MRT

Rational combinations to improve on PSMA MRT monotherapy are being explored in clinical trials. These include $^{177}$Lu-PSMA-617 combined with AR-targeted agents, poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors and other DNA-damaging agents, and immunotherapy. We have recently reviewed ongoing combination trials and their underlying rationale (71).

The efficacy of $^{177}$Lu-PSMA-617 with AR-targeted agents is being investigated in PSMAAddition and in the randomized phase 2 ENZA-P trial (NCT04491402) led by Emmett in Australia. ENZA-P is testing $^{177}$Lu-PSMA-617 plus enzalutamide versus enzalutamide alone, as a first-line treatment in PSMA PET-positive mCRPC.

The PCF-supported LuPARP trial (NCT 03874884), led by Sandhu and Hofman, is investigating $^{177}$Lu-PSMA-617 plus olaparib in mCRPC. In this trial, olaparib is used as a novel radiosensitizer to accentuate tumor DNA damage from $^{177}$Lu.

Sandhu’s team is also leading the phase IbII PRINCE trial (NCT03658447), evaluating pembrolizumab plus $^{177}$Lu-PSMA-617 in PSMA PET-positive mCRPC. In interim analyses (74), this combination was found to have manageable toxicity and promising activity, with 27 of 37 (73%) patients experiencing PSA responses of at least 50%, and 7 of 9 (78%) patients with measurable disease experiencing a partial response. Aggarwal (UCSF) is leading a PCF-supported phase 1b study (NCT03805594) evaluating pembrolizumab plus a single dose of $^{177}$Lu-PSMA-617 in mCRPC. In preliminary results (75), in 18 patients treated on 1 of 3 dose schedules, the overall response rate was 44%, median duration of response has not been reached, and 28% of patients experienced PSA declines of at least 50%. Tagawa and Bander’s team at Weill Cornell have also recently initiated a phase 2 trial of $^{225}$Ac-huJ591 plus pembrolizumab (NCT04946370).
A triple-combination trial, testing $^{177}$Lu-PSMA-617 plus olaparib and pembrolizumab in mCRPC, is being planned by Sandhu and team.

**Future Directions of Theranostics**

The success of PSMA-targeted PET and MRT has spurred a theranostics revolution in prostate cancer. Numerous other PSMA-targeted drug classes are under development, many with PCF support. These include PSMA-targeted CAR-T cells, bispecific antibodies (for example, PSMA $\times$ CD3, PSMA $\times$ CD28), antibody–drug conjugates, nanoparticles, and anticancer vaccines, some of which are based on J591 derivatives. PCF-funded studies are also under way to identify predictive biomarkers for PSMA-targeted treatment responses, mechanisms of resistance to PSMA MRT, and novel treatment combinations.

Other potential theranostic targets for which PCF is funding investigations include fibrolast activation protein, CD46, human kallikrein peptidase 2, and DLL3.

**THE CORNERSTONE ROLE OF PCF IN PSMA THERANOSTICS**

Since 1993, PCF has invested over $28.5 million USD on PSMA research. Key foundational PCF-funded studies included early studies by Heston and Fair’s team on PSMA cloning and characterization (3,5,6), development of J591 theranostics by Bander and Tagawa’s team (13–15,17,18,53,55–57,71), development of [F-18]-DCFPyL by Pomper and Cho’s team (35,36), NDA-enabling studies on [Ga-68]PSMA-11 by Czernin, Hope, Calais, and Fendler’s team (43,45,76), and clinical investigations on $^{177}$Lu-PSMA-617 by Hofman and Sandhu’s team (66) (Fig. 1).

In 2019, PCF provided $5 million to establish the Prostate Theranostics and Imaging Centre of Excellence (ProsTIC) at the Peter MacCallum Cancer Centre. Led by Hofman, ProsTIC aims to accelerate prostate cancer theranostics through pioneering an expanded portfolio of practice-changing clinical studies, providing global education and leadership on theranostics adoption into clinical practice, developing a world-class clinical theranostics infrastructure, and doing discovery work to improve and identify new theranostics strategies. ProsTIC and PCF have co-hosted several global webinars on PSMA theranostics attended by several hundred individuals (https://www.pcf.org/webinars/).

PCF also held 2 PSMA Theranostics Working Group meetings (2017 and 2019) at Weill Cornell Medicine, which convened global experts on PSMA biology and theranostics to discuss the state of the science and critical next steps for PSMA theranostics (31,77).

**CONCLUSION**

PSMA has been established as a target for prostate cancer treatment and imaging, which has culminated thus far in 2 FDA-approved PSMA PET imaging agents. On the basis of the positive results from the VISION trial, $^{177}$Lu-PSMA-617 will likely become the first FDA-approved PSMA-targeting treatment for prostate cancer but will likely not be the last. PCF takes pride in the results for patients that have been supported by over 25 years of continuous funding.

**DISCLOSURE**

The authors are employees of the PCF. The studies cited in references 3, 5, 6, 13–18, 31–36, 43–45, 48–50, 53, 55–57, 64–66, 71, and 75–77 were supported by PCF funding. No other potential conflict of interest relevant to this article was reported.

**REFERENCES**

23. Meaze RC, Dusich CL, Foss CA, et al. $^{[3}N\text{-}[(3\text{-}1\text{-}

---

336 THE JOURNAL OF NUCLEAR MEDICINE • Vol. 63 • No. 3 • March 2022


