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

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Running Title: The History of PSMA Theranostics

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ABSTRACT

Prostate-Specific Membrane Antigen (PSMA) is a credentialed imaging and therapy (theranostic) target for the detection and treatment of prostate cancer. PSMA-targeted positron emission tomography (PET) imaging and molecular radiotherapy (MRT) 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 (PCF) has funded critical and foundational PSMA research that established this theranostic revolution. The history and role of PCF funding in this field will be discussed.

Keywords: theranostics, prostate cancer, PSMA, PET imaging, molecular radiotherapy

NOTEWORTHY

1. PSMA is the most credentialed target for prostate cancer imaging and therapy.
2. PSMA PET is a highly sensitive and specific prostate cancer imaging technology with two FDA-approved agents to date.
3. The phase 3 VISION trial demonstrated life-prolonging efficacy of PSMA-targeted MRT and is anticipated to lead to FDA-approval.
4. Since 1994, PCF has funded many foundational advancements in PSMA biology and clinical applications.

INTRODUCTION

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

I. BIRTH – DISCOVERY AND EARLY CHARACTERIZATION

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

Using 7E11-C5, Warren Heston with William Fair at Memorial Sloan Kettering Cancer Center cloned the PSMA gene in 1993 (*2,3*). PSMA, also known as folate hydrolase 1 (FOLH1) and glutamate carboxypeptidase II (GCP-II), is a 750-amino acid, 100kD, type II transmembrane protein, with a short N-terminal intracellular domain and a large C-terminal extracellular domain (*2*). PSMA is predominantly expressed in the prostate and a subset of proximal renal tubules, with lower level expression in small bowel, salivary glands and some glial cells in the brain (*1-5*). In 1993, Heston concluded that "as an integral membrane protein unique to prostatic epithelial cells, the antigen or perhaps a specific PSM[A] ligand may serve as an excellent site for imaging and/or targeting of metastatic deposits," setting the stage for PSMA as a theranostic target (*2*).

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

II. YOUTH – EARLY EVIDENCE OF UTILITY

ANTI-PSMA ANTIBODY DEVELOPMENT

Development of 7E11-C5 as a theranostic agent began prior to identification of PSMA as its target (*8,10,11*). In 1996, ^{111}In-capromab pendetide (ProstaScint®) 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 Neil Bander and colleagues at Weill Cornell Medical College (*13*). J591, the lead antibody, enabled studies of PSMA in viable cells. Bander's team demonstrated that PSMA is constitutively internalized, and antibody-binding increased the rate of internalization by several-fold (*14*). 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" (*14*).

David Scheinberg (Memorial Sloan Kettering Cancer Center) received PCF-funding to develop alpha particle-emitting antibody-molecular radiotherapy (MRT) constructs for prostate cancer. With Bander, Scheinberg and colleagues demonstrated preclinical activity for ^{213}Bi-J591 and ^{225}Ac-J591 conjugates (*15,16*). Bander and colleagues further demonstrated promising anti-tumor efficacy of beta-emitting conjugates ^{90}Y-J591 and ^{177}Lu-J591 in preclinical models (*17*).

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

PSMA-TARGETED LIGAND DEVELOPMENT

In 2001, Alan Kozikowski et al. (Georgetown University) developed urea-based inhibitors of the neurotransmitter regulator GCP-II (NAALADase), a central nervous system version of PSMA, as potential neuroprotective agents (*19*). The urea-based motif (glutamate-urea-lysine) binds with high affinity to the extracellular domain of GCP-II (PSMA) (*20*). Martin Pomper (Johns Hopkins University) 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 (*21*). Pomper led the first *in vivo* animal studies evaluating GCP-II-targeted urea-based ligands as PET and SPECT agents (*21,22*). Pomper and colleagues 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" (*22*). Most currently studied PSMA-targeted ligands are derivatives of these early urea-based compounds.

Pomper and colleagues further developed PSMA-targeted PET imaging ligands ^{18}F-DCFBC in 2008 (*23*), and ^{18}F-DCFPyL (PyL) in 2011 (*24*), as well as the first 68-gallium-labeled PSMA-targeted ligands in 2010 (*25*).

The PET tracer ^{68}Ga-PSMA-11 (^{68}Ga-PSMA-HBED-CC; ^{68}Ga-DKFZ-PSMA-11) was developed by Matthias Eder (German Cancer Research Center) and colleagues and published on in 2012 (*26*).

^{18}F-DCFPyL and ^{68}Ga-PSMA-11 are the most studied PSMA-targeted PET tracers. Both have recently been FDA-approved. Clinical development of these is discussed below.

Development and promising first clinical experiences with the PSMA-targeted ligand ^{177}Lu-PSMA-DOTAGA-FFK(Sub-KuE) (PSMA-TUM1) and its improved derivative PSMA I&T, were reported in 2014 and 2015, respectively, by Richard Baum (Zentralklinik Bad Berka), Martina Weineisen (Technische Universität München) and colleagues (*27,28*).

In 2015, Eder, Clemens Kratochwil (University Hospital Heidelberg), and colleagues reported development and first clinical experiences with PSMA-targeting ligand PSMA-617 (*29,30*). ^{68}Ga-PSMA-617 showed promise as a PET tracer (*29*), and the first mCRPC patient treated with ^{177}Lu-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*).

III. ADOLESCENCE – TRANSLATION

CLINICAL DEVELOPMENT OF PSMA-PET

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

^{18}F-DCFPYL PET

^{18}F-DCFBC was the predecessor of ^{18}F-DCFPyL. In early PCF-funded clinical studies led by Pomper, Steve Cho, and colleagues, ^{18}F-DCFBC outperformed ^{99}mTc-methylene diphosphonate (MDP) 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, ^{18}F-DCFBC PET was less sensitive for detecting primary prostate cancer, but more specific for clinically significant lesions (*34*).

^{18}F-DCFPyL has higher PSMA binding affinity and lower blood pool activity than ^{18}F-DCFBC and became the agent of choice for additional PCF-funded clinical development at Johns Hopkins. The first clinical experience with ^{18}F-DCFPyL, reported in 2015, demonstrated safety, significant tumor-specific uptake, and expected tissue biodistribution (*35*). ^{18}F-DCFPyL was superior to bone scan and CT in a lesion-by-lesion comparative study (*36*). In subsequent phase 2 trials, some supported by PCF, ^{18}F-DCFPyL showed impressive performance for initial staging and for detecting biochemical recurrence (BCR) (*31*). In 2015, ^{18}F-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 Kenneth Pienta (Johns Hopkins University) and Michael Morris (Memorial Sloan Kettering Cancer Center), ^{18}F-DCFPyL PET/CT

demonstrated 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 95.8% sensitivity and 81.9% positive predictive value (PPV) for detecting metastases in patients with suspected recurrent/metastatic lesions seen on conventional imaging (*37*). In the phase 3 CONDOR trial (NCT03739684), led by Morris, ^{18}F-DCFPyL PET/CT correctly localized prostate cancer metastases in 85% of patients with BCR, based on comparison with composite standard-of-truth, and changed planned management in 64% of patients (*38*). Results from OSPREY and CONDOR led to FDA-approval for ^{18}F-DCFPyL PET (PYLARIFY®) 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 elevated serum PSA level (*39*).

^{68}GA-PSMA-11 PET

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

The first clinical PET/CT imaging experience with ^{68}Ga-PSMA-11 was reported in 2012 by Christian Zechmann (University Hospital Heidelberg) (*40*). Meta-analyses of ^{68}Ga-PSMA-11 PET from 4,790 patients across 37 publications estimated a detection rate of 95%, 75%, 59%, 45%, and 33% for PSA levels ≥2, 1–1.99, 0.5–0.99, 0.2–0.49, and 0–0.19 ng/ml, respectively (*41*).

In 2016, Michael Hofman and Declan Murphy (Peter MacCallum Cancer Centre, Australia) initiated the first randomized study of ^{68}Ga-PSMA-11 PET (ProPSMA study). This 10-centre, 300 patient, phase 3 study demonstrated a 29% absolute improved accuracy of PSMA PET compared to CT/bone scan (*42*).

A PCF-funded UCLA-UCSF team led by Thomas Hope, Johannes Czernin, Jeremie Calais, and Wolfgang Fendler, conducted two prospective NDA-enabling trials for ^{68}Ga-PSMA-11 PET. In patients with BCR (NCT02940262, NCT03353740), lesion detection rates with ^{68}Ga-PSMA-11 PET were 97%, 86%, 84%, 57%, and 38% for PSA levels ≥5.0, 2.0 - 5.0, 1.0 - 2.0, 0.5 -1.0, and <0.5 ng/mL, respectively. PPV was 92% by composite validation assessment (*43*). A phase 3 study (NCT03368547) investigating ^{68}Ga-PSMA-11 in pre-surgical patients with intermediate to high-risk prostate cancer, reported 40% sensitivity and 95% specificity for detection of pelvic nodal metastases (*44*). This team also demonstrated superiority of ^{68}Ga-PSMA-11 over ^{18}F-fluciclovine PET/CT in patients with BCR at low PSA levels (<2.0 ng/mL) in a prospective comparison (NCT03515577) (*45*). In December 2020, ^{68}Ga-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 make ^{68}Ga-PSMA-11 to file an Abbreviated NDA (*46*). The entirely academic development of ^{68}Ga-PSMA-11 is a noteworthy achievement, and PCF was proud to have funded the UCSF-UCLA teams.

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 Phuoc 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 (PFS) 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 ^{177}Lu-PSMA-617.

Several other PSMA PET agents are under development. These include ^{18}F-PSMA-1007 and ^{18}F-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 ^{18}F- and ^{68}Ga-based PSMA PET imaging. These include PSMA-RADS, developed with PCF-support by Steven Rowe (Johns Hopkins University), Pomper and colleagues, which is now included in the umbrella system Molecular Imaging Reporting and Data Systems (MI-RADS) (*49*).

Limitations of PSMA PET have previously been detailed (*31*), and include loss of PSMA expression in some patients with advanced CPRC/NEPC, heterogeneity in PSMA expression, and resolution limits.

PSMA PET AS AN IMAGING AGENT IN OTHER CANCERS

Due to expression of PSMA on tumor vasculature, PSMA PET may have potential for imaging other cancer types. In a PCF-funded study in five patients with metastatic renal cell carcinoma, ^{18}F-DCFPyL PET/CT exhibited a sensitivity of 94.4% and identified more putative metastatic lesions than conventional imaging (*50*). An ongoing trial is further testing ^{18}F-DCFPyL PET/CT in renal cell carcinoma (NCT02687139).

CLINICAL DEVELOPMENT OF PSMA-TARGETED MOLECULAR RADIOTHERAPY (MRT)

The first PSMA-targeted radionuclide tested as a therapeutic agent in prostate cancer patients, was 7E11-C5.3 (^{90}Y-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, David Nanus, Scott Tagawa and colleagues (Weill Cornell Medical College) initiated a series of phase 1 and 2 trials testing huJ591-based MRT in advanced prostate cancer, several of which were PCF-supported. These studies represented the first clinical use of ^{177}Lu as a systemically administered agent, and demonstrated safety, accurate targeting of metastatic prostate cancer sites, and preliminary anti-tumor activity for ^{90}Y-huJ591 and ^{177}Lu-huJ591, providing the first direct clinical evidence supporting the potential of PSMA-targeted MRT (*53-55*).

Bander's team also demonstrated safety, feasibility and promising activity with dose-fractionated ^{177}Lu-huJ591, with higher cumulative doses associated with longer median overall survival (OS) and increased myelosuppression (*56*). In another PCF-funded trial, fractionated ^{177}Lu-huJ591 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 ^{177}Lu-PSMA-TUM1 and ^{131}I-MIP-1095; anti-tumor activity for both were reported in 2014 (*27,58*).

CLINICAL DEVELOPMENT OF ^{177}LU-PSMA-617

Following their 2015 report on an individual patient treated with ^{177}Lu-PSMA-617 (discussed above) (*30*), in 2016 Kratochwil et al. reported on 30 patients with PSMA PET-positive mCRPC treated with 1-3 cycles of ^{177}Lu-PSMA-617. 43% experienced a PSA reduction ≥50% (*59*). In a multicenter retrospective report evaluating 145 patients treated at German centers, PSA declines ≥50% were observed in 45% of patients (*60*).

The first prospective trial testing ^{177}Lu-PSMA-617 was led by Hofman and colleagues at the Peter MacCallum Cancer Centre in Australia (LuPSMA trial; ACTRN12615000912583) (*61,62*). This single-arm phase 2 trial enrolled 50 PSMA PET-positive mCRPC patients who had failed conventional therapies. Patients with PSMA-negative/FDG PET-positive lesions were excluded. Patients received up to 4 doses of ^{177}Lu-PSMA-617 (mean radioactivity 7.5 GBq) every ~6 weeks. 64% of patients experienced PSA reductions ≥50% (*61,62*). Quality of life measures including pain severity were improved. Unfortunately, all 50 patients eventually progressed. The trial results led to Endocyte's (now Novartis) acquisition of PSMA-617 from ABX GmbH which accelerated commercial development including the phase 3 VISION trial (*63*).

A PCF-supported randomized phase 2 trial, led by Czernin and Calais at UCLA, tested up to 4 cycles of 6.0 GBq vs. 7.4 GBq of ^{177}Lu-PSMA-617, every 8 weeks, 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 ≥50% and the median OS was 14.0 months (*64*).

A PCF-supported phase 1/2 trial led by Bander and Tagawa tested dose-fractionated ^{177}Lu-PSMA-617 in unselected mCRPC patients (NCT03042468). No maximum tolerable dose or dose-limiting toxicities were observed with one cycle of fractionated cumulative doses of 7.4 to

22 GBq (*65*). Of 44 patients treated, 59.1% had a >50% PSA decline, and median OS was 16 months (*65*). Of note, this is the only conventional dose-escalation trial done for ^{177}Lu-PSMA-617.

IV. ADULT = THERANOSTICS REVOLUTION

The phase 2 TheraP trial (NCT03392428; ANZUP 1603) led by Hofman, was the first randomized trial comparing ^{177}Lu-PSMA-617 to a standard treatment in mCRPC, cabazitaxel. This trial enrolled 200 patients with PSMA PET-positive mCRPC with no PSMA-negative/FDG PET-positive lesions (out of 291 screened by PET (69%)), who had previously progressed on docetaxel (91% had prior abiraterone or enzalutamide). The primary endpoint, ≥50% PSA decline, was experienced by significantly more patients treated with ^{177}Lu-PSMA-617 (66%) vs. cabazitaxel (44%) (*66*). Analysis of secondary endpoints are ongoing. Grade 3-4 TEAEs were lower among patients treated with ^{177}Lu-PSMA-617 (33%) vs. cabazitaxel (53%) (*66*).

The Novartis/Endocyte-sponsored international randomized open-label phase 3 VISION trial (NCT03511664), testing ^{177}Lu-PSMA-617 plus protocol-permitted standard of care (SOC; excluding chemotherapy, immunotherapy, radium-223, and investigational drugs) vs. SOC alone (randomized 2:1) was initiated in 2018, led by Morris and Oliver Sartor (Tulane University). The trial enrolled 831 patients with PSMA PET-positive mCRPC who had previously progressed on docetaxel and an anti-androgen therapy. ^{177}Lu-PSMA-617 dosing consisted of 7.4 GBq every 6 weeks for four to six cycles. The trial initially suffered from significant control arm attrition, which was reduced upon implementation of enhanced trial-site education. Radiographic PFS (rPFS) analysis included only patients enrolled after education measure implementation (N = 581), while OS analysis included all 831 patients (*67*). The addition of ^{177}Lu-PSMA-617 to SOC significantly prolonged both alternate primary endpoints; median OS (15.3 vs. 11.3 months; HR, 0.62), and median rPFS (8.7 vs. 3.4 months; HR, 0.40) (*67*). All key secondary endpoints significantly favored ^{177}Lu-PSMA-617, including time to first symptomatic skeletal event (median, 11.5 vs. 6.8 months), objective response rate (29.8% vs. 1.7%), and disease control rate (89.0% vs. 66.7%) (*67*). Complete responses occurred in 9.2% of patients with measureable disease in the ^{177}Lu-PSMA-617 arm vs. none in the control arm and partial responses occurred in 41.8% of patients in the ^{177}Lu-PSMA-617 arm vs. 3% in the control arm (*67*). While a higher rate of Grade ≥3 AEs were observed with ^{177}Lu-PSMA-617 (52.7% vs 38.0%), health-related quality-of-life scores were improved (*67*). The most common TEAEs in the ^{177}Lu-PSMA-617 group were fatigue, dry mouth, and nausea, nearly all being Grade 1-2 events (39% experienced Grade 1-2 dry mouth with no Grade ≥3 events) (*67*). Five Grade 5 drug-related deaths occurred in the ^{177}Lu-PSMA-617 arm (*67*). Based on these data, ^{177}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}Lu-PSMA-617 in earlier disease settings. PSMAfore (NCT04689828) is testing ^{177}Lu-PSMA-617 vs. a change in AR-targeted therapy in taxane-naïve mCRPC patients that previously progressed on an alternate AR-targeted therapy. PSMAddition (NCT04720157) is testing ^{177}Lu-PSMA-617 plus SOC (AR-targeted

therapy + ADT) vs. SOC alone in patients with metastatic hormone sensitive prostate cancer. The primary endpoint for both studies is rPFS.

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

OTHER BETA-EMITTING PSMA MRTS UNDER DEVELOPMENT

In addition to ^{177}Lu-PSMA-617 and ^{177}Lu-huJ591, several other beta-emitting PSMA-targeted MRTs are under development.

Those include ^{177}Lu-PSMA-I&T (PNT2002, POINT Biopharma) which is being tested in the phase 3 SPLASH trial in patients with PSMA PET-positive mCRPC who have progressed on AR-targeted therapy (NCT04647526). This two-part study consists of a safety and dosimetry lead-in, followed by a randomization phase comparing ^{177}Lu-PSMA-I&T vs. abiraterone or enzalutamide.

^{177}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 vs SOC alone, in patients with PSMA PET-positive mCRPC who have progressed on AR-targeted therapy.

CLINICAL DEVELOPMENT OF ALPHA-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}AC-PSMA-617

In 2016, Kratochwil, Alfred Morgenstern (Institute for Transuranium Elements) and colleagues reported on two mCRPC patients treated with ^{225}Ac-PSMA-617 who experienced complete PSA and imaging responses (*68*). Moderate to severe xerostomia was the only TEAE reported (*68*). In 2018, the group published on 40 consecutive mCRPC patients treated with up to 3 cycles of ^{225}Ac-PSMA-617 (*69*). Of 38 patients who survived over 8 weeks, 63% experienced PSA declines ≥50% (*69*). Five patients (13%) had complete PSA responses enduring over 2 years (*69*).

Promising anecdotal clinical experiences with ^{225}Ac-PSMA-617 have also been reported by groups in Germany, India, and South Africa. The first planned clinical trials with ^{225}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

Due to the larger molecular mass of J591 and lack of detectable uptake in the salivary and lacrimal glands (*70*), Bander, Tagawa, and colleagues hypothesize that ^{225}Ac-huJ591 could deliver promising anti-tumor 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 32 mCRPC patients unselected by PSMA-PET (NCT03276572), ^{225}Ac-huJ591 was well tolerated, with no maximum tolerable dose reached (*71*). 19 of 32 (59%) patients experienced any PSA decline and 14 (44%) experienced ≥50% PSA decline (*71*). 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 different site on PSMA than 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 Thorium-227-labeled anti-PSMA antibody ^{227}Th-PSMA-TTC (BAY 2315497, Bayer), which is in a phase I study in mCRPC (NCT03724747). ^{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 extended serum half-life, developed by John Babich (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 upon PSMA-MRT monotherapy are being explored in clinical trials. These include ^{177}Lu-PSMA-617 combined with AR-targeted agents, PARP-inhibitors and other DNA damaging agents, and immunotherapy. We have recently reviewed ongoing combination trials and their underlying rationale (*31*).

The efficacy of ^{177}Lu-PSMA-617 with AR-targeted agents is being investigated in PSMAddition (discussed above), and in the randomized phase 2 ENZA-P trial (NCT04419402)

led by Louise Emmett in Australia. ENZA-P is testing ^{177}Lu-PSMA-617 plus enzalutamide vs enzalutamide alone, as a first-line treatment in PSMA PET-positive mCRPC.

The PCF-supported LuPARP trial (NCT03874884), led by Shahneen 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 and team are also leading the phase Ib/II PRINCE trial (NCT03658447), evaluating pembrolizumab plus ^{177}Lu-PSMA-617 in PSMA PET-positive mCRPC. In interim analyses, this combination was found to have manageable toxicity and promising activity, with 27/37 (73%) patients experiencing PSA responses ≥50%, and 7/9 (78%) patients with measurable disease experiencing a partial response (*74*). Rahul Aggarwal (University of California, San Francisco) 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, in 18 patients treated on one 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 ≥50% (*75*). Tagawa, Bander and colleagues 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 have 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, bi-specific antibodies (PSMA x CD3), antibody-drug conjugates, nanoparticles, and anti-cancer vaccines, some of which are based on J591-derivatives. PCF-funded studies are also underway to identify predictive biomarkers for PSMA-targeted treatment responses, mechanisms of resistance to PSMA MRT, and novel treatment combinations.

Other possible theranostic targets that PCF is funding investigations into include fibroblast activation protein (FAP), CD46, human kallikrein peptidase 2 (hK2), and DLL3.

V. THE FUNDAMENTAL 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 Heston, Williams and colleagues' early studies on PSMA cloning and characterization (*3,5,6*), development of J591 theranostics by Bander, Tagawa, and colleagues (*13-15,17,18,53,55-57,71*), Pomper and Cho's development of ^{18}F-DCFPyL (*35,36*), Czernin, Hope, Calais and Fendler's NDA-enabling studies on ^{68}Ga-PSMA-11

(*43,45,76*), and Hofman, Sandhu and team's clinical investigations on ^{177}Lu-PSMA-617 (*66*) **(Figure 1)**.

In 2019, PCF provided $5 million USD to establish The Prostate Theranostics & 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 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 two PSMA Theranostics Working Group meetings (2017, 2019) at Weill Cornell Medicine, which convened global experts on PSMA biology and theranostics to discuss the state of 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 two FDA-approved PSMA PET imaging agents. Based on 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.

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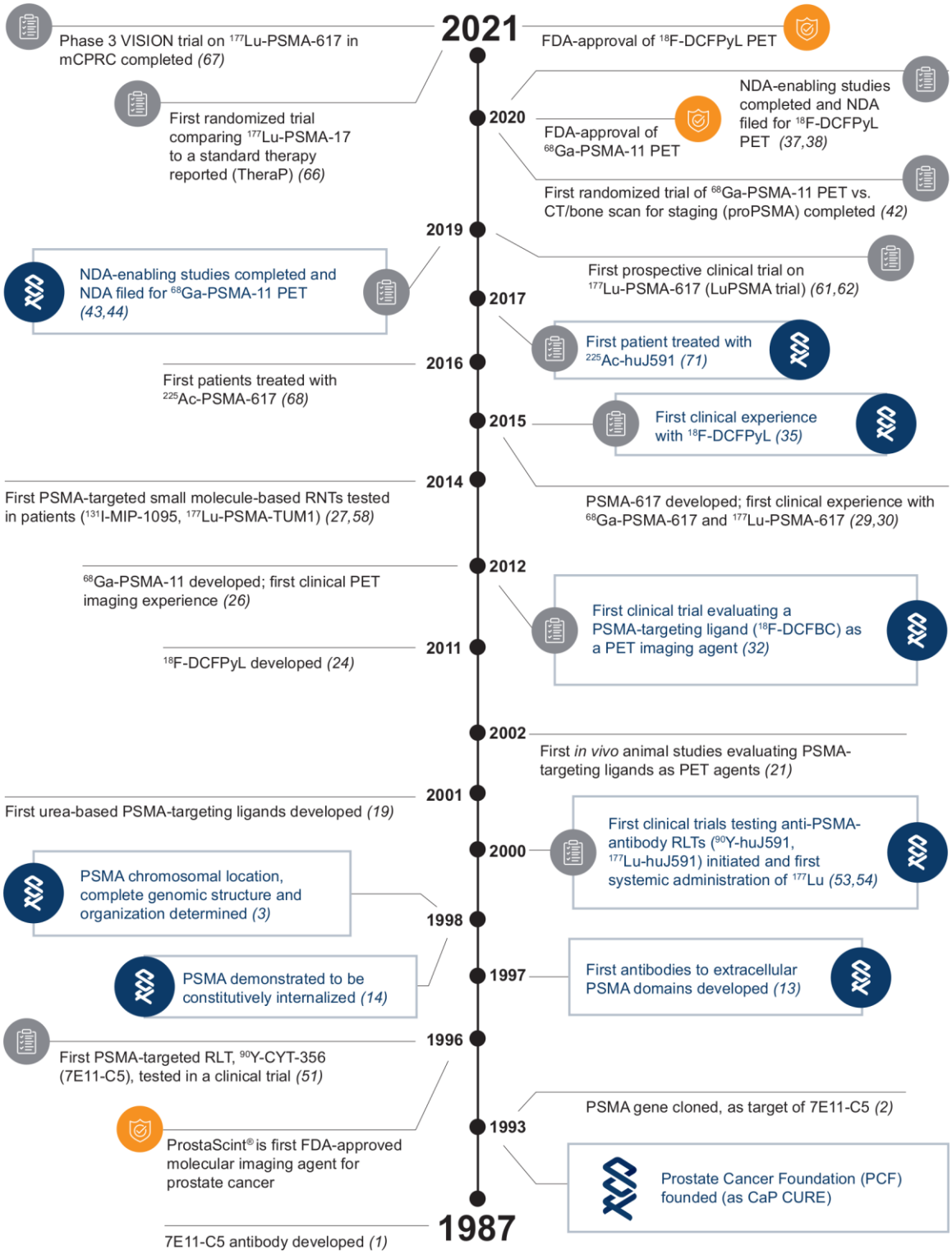

Figure 1. Timeline of major milestones in the development of PSMA theranostics. Research achievements that were supported by PCF-funding are indicated by blue font and the PCF logo. Dates typically denote year of publication.