

# PSMA Protein Showing Its Mettle in the Battle Against Prostate Cancer

Despite the rapid advances we have witnessed in the detection and treatment of prostate cancer in recent years, prostate cancer remains the second leading cause of cancer death among men globally<sup>1</sup>. As such, expanding our knowledge of disease pathology and related biomarkers is still sorely needed. To this end, a unique recombinant protein known as **prostate-specific membrane antigen (PSMA)**, manufactured by **Bio-Techne** brand R&D systems, could offer a beacon of hope for patients and clinicians alike.

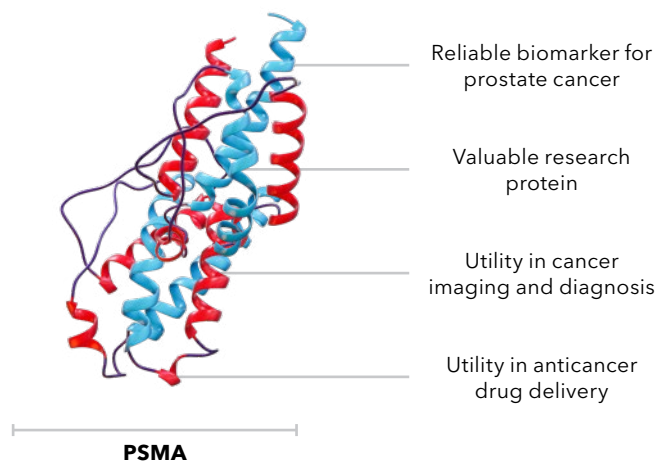


FIGURE 1. Protein structure of PSMA molecule highlighting some of its key attributes, and current applications.

The PSMA protein is a surface membrane protein expressed in high concentrations in the prostate, and is upregulated by 100-1000 fold in prostate tumors<sup>2</sup> - making it a highly specific biomarker and therapeutic target. Now clinically validated, PSMA has become one of the most exciting biomarkers for prostate cancer, and is proving to be a valuable tool for prostate cancer research, while also showing promise in anticancer drug delivery (FIGURE 1).

In recent years, there has been an increased focus on PSMA research, with studies demonstrating the

wide utility of this exciting protein in **cancer research**, diagnostic imaging, and targeted anticancer treatment. Here we will take a look at some of the current insights into PSMA, and its growing role in the fight against prostate cancer and beyond.

## Role of PSMA in Prostate Cancer

The carcinogenesis of prostate cancer has been strongly linked to the regulation of folate (vitamin B9) in the organ. It is thought that PSMA plays a direct role in folate uptake, with folate itself, and many other PSMA-specific ligands becoming internalized upon binding<sup>3</sup>. By increasing intracellular folate concentration, the protein actively promotes tumor growth. The cancer-promoting activity of PSMA is compounded by the upregulation of the protein: The upregulation of PSMA creates more opportunities for folate to bind and become internalized, thereby driving disease progression further. As such, PSMA can be considered a highly specific target when it comes to prostate cancer therapeutics.

## Recombinant PSMA Protein in Preclinical Research

The availability of recombinant PSMA has provided a platform to enhance our understanding of the functions and behaviour of the prostate in a healthy setting, and has helped to uncover the complex processes involved in prostate tumor progression. Furthermore, the commercial availability of recombinant PSMA has enabled the identification/generation of monoclonal antibodies, aptamers and small molecules that can target the protein for imaging or therapeutic purposes<sup>4</sup>.

## Value of PSMA in Imaging and Diagnostics

Thanks to its unique expression pattern in prostate cancers, PSMA provides value in the detection and staging of the disease. Conventionally, imaging techniques for prostate cancer include a combination of bone scintigraphy, CT, and MRI scans. While functional, these traditional methods are being challenged by emerging research into PSMA-specific PET scans (PSMA-PET), which, according to a number of studies, enables much improved detection rates and superior diagnostic accuracy<sup>5</sup>.

A large number of antibody- and ligand-based PSMA-PET agents have been developed, with the US Food and Drug Administration (FDA) having approved several PSMA-PET imaging drugs<sup>6</sup>. PSMA-PET has proved successful in clinical trials, where management plans for patients with prostate cancer changed more often with PSMA-PET than with traditional imaging methods<sup>7</sup>. PSMA-PET is useful beyond initial diagnosis too, and can be worthwhile at multiple timepoints throughout the disease course, from initial staging of high-risk disease to monitoring the effects of therapy. The success of PSMA-PET for imaging and diagnostics stands testament to PSMA's high specificity as a prostate cancer biomarker and therapeutic target.

Elsewhere on the prostate cancer diagnostics front, [Exosome Diagnostics](#), a Bio-technique brand, has developed a simple test to detect key biomarkers associated with the disease. The diagnostic was launched in 2016 and is now included in the National Comprehensive Cancer Network (NCCN) guidelines for early prostate cancer detection. The [ExoDx™ Prostate IntelliScore EPI](#) (EPI test) is the world's first exosome-based diagnostic test; tumor RNA is detectable in exosomes released from the prostate into the urine, and as such, key disease biomarkers can be detected with a simple urine test. Speaking about the novel test, Johan Skog, Chief Scientific Officer at Exosome Diagnostics said:

“Exosomes have really revolutionized the way we look at biomarkers. We can get access to tumour specific molecular content such as RNA through non-invasive means such as a regular urine sample. The current EPI test is not looking at PSMA, but it is known that PSMA can be found on the surface of prostate exosomes, and there is a lot of interest around how PSMA on exosomes can further improve the diagnostic tests for prostate cancer”

## PSMA in Targeted Cancer Therapy

The success of PSMA-PET in the accurate detection of prostate cancer has given rise to novel radiotherapy techniques to fight the disease. Radiotherapy can be a curative measure for patients with newly diagnosed localized prostate cancer, those with recurrences after radical prostatectomy, and individuals with metastatic disease<sup>8</sup>.

PSMA is an ideal candidate for a radiotherapy target. Since PSMA is overexpressed in the tumor compared with normal tissues, active radiotherapy doses can be delivered to the target tissue with diminished side effects. PSMA-targeted radiotherapy can also overcome obstacles brought about by heterogeneous target expression, that regularly exists between tumors. By targeting a ubiquitous prostate cancer protein, PSMA-targeted radiotherapy can be beneficial for a wide range of patient phenotypes.

In various clinical trials, PSMA targeted radiotherapy has shown overwhelmingly positive results, providing a last line of defence for patients with aggressive late-stage disease. For example, in individuals with castration-resistant prostate cancer, a situation where cure is no longer achievable, PSMA-targeted radiotherapy has helped to prolong survival and aid in palliative care<sup>9</sup>. Such was the success of clinical trials, that the US FDA approved the use of PSMA radiotherapy agent <sup>177</sup>Lu-PSMA-617 for patients with castration-resistant prostate cancer.

## An Exciting Biomarker for Prostate Cancer and Beyond

The PSMA protein has transformed prostate cancer research, providing a highly-specific target for imaging and therapeutics. The success of PSMA-targeted radiotherapy in clinical trials has provided proof of concept that targeting this surface membrane protein can be effective in the clinic.

Emerging research supports the wider adoption of PSMA-PET in the diagnosis, staging, disease burden evaluation and response monitoring of prostate cancer. And diagnostic tools like the EPI test from Exosome Diagnostics are already helping to diagnose the disease much earlier. There is much left to do on the therapeutic side however - most of the clinical research into PSMA agents has been conducted on late-stage patients with little chance of survival. Current trials are under way to assess not only greater efficacy but also longer-term toxicity among patients with earlier-stage disease and longer life expectancy.

Overall, the evidence indicates that PSMA-based treatments hold great promise for addressing the continued need for effective prostate cancer treatments, but more research is required at the preclinical and clinical level to discover novel and effective ways to utilize this highly conserved protein target.

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