



Clinical Trials Using Prostate-Specific Membrane Antigens

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DESCRIPTION

The most well-known and highly specific prostate epithelial cell membrane antigen is Prostate-Specific Membrane Antigen (PSMA). Chromosome 11p has been identified by the cloning of PSMA and determining its sequence. According to pathology investigations, almost all prostate tumours express PSMA. Additionally, PSMA expression gradually rises in metastatic illness, higher-grade tumours, and Castration-Resistant Prostate Cancer (CRPC). Despite being initially believed to be totally prostate-specific, later research revealed that PSMA is also expressed by cells in the small intestine, proximal renal tubules, and salivary glands.

Importantly, the expression is 100-1000 times lower in normal cells than it is in prostate tissue, and the expression location is rarely exposed to circulating complete antibodies. Furthermore, unlike the natural vasculature, the vast majority of solid tumour malignancies display PSMA in the neovasculature. PSMA is an integral cell-surface membrane that do not secrete proteins, in contrast to other well-known prostate-restricted molecules like Prostate-Specific Antigen (PSA) and Prostate Acid Phosphatase (PAP), which are secretory proteins. This makes PSMA an ultimate target for Monoclonal Antibody (mAb) therapy.

The activities of neurocarboxypeptidase and folate hydrolase has been discovered in prostate-specific membrane antigen. The constant observation that PSMA overexpression correlates with higher cancer aggressiveness suggests that PSMA plays a functional role in PC progression, even if its function in Prostate Cancer (PC) biology is unknown. *In vitro* or in xenograft models, inhibiting enzymatic activity hasn't been shown to have a major growth-inhibitory effect. However, the PSMA expression pattern makes it a prime candidate for PC-targeted mAb therapy.

Using radiolabeled mAb 7E11, prostate-specific membrane antigen was first verified as an *in vivo* imaging target (CYT-356, capromab). Patients who come with Gleason scores greater than 6 and those who experience a rising PSA following prostatectomy can use capromab pentetide imaging to determine the extent of the disease. Despite advancements in Single-Photon Emission Computed Tomography (SPECT) and

SPECT/CT imaging, this imaging technology has not been widely used due to capromab pentetide's poor sensitivity and specificity. According to molecular mapping, a region of PSMA which is inside the cell and not exposed on the outer cell surface and that cannot bind to viable cells was the target of 7E11. Recognising these features, a study was led to the development of mAbs to the exposed, extracellular domain of PSMA. Theoretically, the mAbs linked to the PSMA would significantly enhance *in vivo* targeting, likely results in improved imaging and therapeutic effects. Following testing, these antibodies (J591, J415, J533, and E99) in fact show highly-affine binding to PSMA-expressing LNCaP cells that were still able to divide. They were also quickly internalised. The deimmunized IgG monoclonal antibody known as J591 was the most clinically advanced of these antibodies.

A radionuclide is joined to a Monoclonal Antibody (mAb) or peptide and commonly administered systemically in Radioimmunotherapy (RIT). In clinical practice, radionuclides that are often beta-emitters can be used to mark mAbs and peptides. This "targeted" method of RT enables the delivery of radiation to malignancies while protecting healthy tissues. In the earliest type of RIT, solid tumours were treated with radiolabeled antibodies against carcinoembryonic antigen.

The most researched type of RIT to date focuses on the CD20 antigen in non-lymphoma Hodgkin's and has been approved by the FDA after proving safety and efficacy in phase I-III trials. It has taken longer for RIT to develop for solid-tumor cancers.

Numerous factors contribute to this, including the absence of specialised antigens and antibodies that are tailored for RIT, challenges in securely tying radionuclides to already-existing mAbs, shortcomings in currently-used (and easily accessible) radionuclides, and challenges in clinical application (coordination between different specialties). However, RIT-based clinical trials for solid-tumor malignancies have been growing. One dose of radioimmunotherapy or several fractions can be administered. Following the injection of radiolabeled mAbs, the extent of the antitumor response is influenced by a number of factors, particularly the total cumulative radiation dosage to the tumour, dose rate, and tumour radiosensitivity.

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CONCLUSION

PSMA is the best target for mAb-directed therapy in the treatment of prostate cancer. Anti-PSMA mAbs have been successfully used in the past to deliver toxic payloads to PC cells only, reducing harm to healthy organs. Current approaches aim to build on these accomplishments. Anti-PSMA RIT and Antibody-Drug Conjugate

(ADC) technologies have been used in clinical settings to date. Anti-PSMA vaccinations and using PSMA-targeted therapy with or without other immune modulators to promote anti-PSMA and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) are two more projects that are still in the early phases of development.