

Murine Six-Transmembrane Epithelial Antigen of the Prostate, Prostate Stem Cell Antigen, and Prostate-specific Membrane Antigen: Prostate-specific Cell-Surface Antigens Highly Expressed in Prostate Cancer of Transgenic Adenocarcinoma Mouse Prostate Mice¹

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ABSTRACT

To identify genes that are differentially up-regulated in prostate cancer of transgenic adenocarcinoma mouse prostate (TRAMP) mice, we subtracted cDNA isolated from mouse kidney and spleen from cDNA isolated from TRAMP-C1 cells, a prostate tumor cell line derived from a TRAMP mouse. Using this strategy, cDNA clones that were homologous to human six-transmembrane epithelial antigen of the prostate (*STEAP*) and prostate stem cell antigen (*PSCA*) were isolated. Mouse *STEAP* (*mSteap*) is 80% homologous to human *STEAP* at both the nucleotide and amino acid levels and contains six potential membrane-spanning regions similar to human *STEAP*. Mouse *PSCA* (*mPscA*) shares 65% homology with human *PSCA* at the nucleotide and amino acid levels. mRNA expression of *mSteap* and *mPscA* is largely prostate-specific and highly detected in primary prostate tumors and metastases of TRAMP mice. Both *mSteap* and *mPscA* map to chromosome 5. Another known gene coding for mouse prostate-specific membrane antigen (*mPsmA*) is also highly expressed in both primary and metastatic lesions of TRAMP mice. These results indicate that the TRAMP mouse model can be used to effectively identify genes homologous to human prostate-specific genes, thereby allowing for the investigation of their functional roles in prostate cancer. *mSteap*, *mPscA*, and *mPsmA* constitute new tools for preventative and/or therapeutic vaccine construction and immune monitoring in the TRAMP mouse model that may provide insights into the treatment of human prostate cancer.

INTRODUCTION

Prostate cancer is the most common malignancy and the second leading cause of cancer death in men in North America. The serum PSA³ test has revolutionized the early detection of prostate cancer and has resulted in enthusiasm to identify additional novel and increasingly specific markers in prostate cancer. Progress in identifying such markers has been markedly accelerated by recent advances in molecular biology technologies, such as differential display analysis, subtraction approaches, and microarray techniques. These techniques and others have led to the identification of more than 20 genes with prostate-specific/abundant expression (1–20), such as *PSMA* (3), *PSCA* (9), and *STEAP* (12). Given their cancer/prostate-specific distributions, these genes theoretically encode targets suitable for implementation in therapies of prostate cancer. However, the development of such therapies has been severely limited by the absence of an

animal model that closely mimics human prostate cancer and expresses the prostate-specific genes under study at physiologically relevant levels.

The recent development of a spontaneous transgenic mouse model of prostate cancer, TRAMP (21), and the isolation of syngeneic transplantable prostate cancer cell lines (TRAMP-C1 and -C2) derived from TRAMP prostate tumors (22) has provided much needed model systems to comprehensively test various experimental prostate cancer therapies. Hence, to identify genes specifically or overexpressed in TRAMP prostate tumors, we used a SSH³ to subtract cDNA derived from mouse kidney and spleen from cDNA isolated from TRAMP-C1 cells. Using this strategy, cDNA clones homologous to human *STEAP* (12) and *PSCA* (9) were obtained. *mSteap* and *mPscA* have similar tissue distributions as human *STEAP* and *PSCA* and are highly expressed in primary and metastatic lesions in TRAMP mice. Another known gene, *mPsmA* (23), was also highly detected in this study in both primary and metastatic cancers of TRAMP mice. These murine prostate-specific genes combined with the TRAMP model may provide a useful animal model system to investigate therapeutic strategies against prostate cancer.

MATERIALS AND METHODS

Cell Lines and Mouse Tissues. The TRAMP-C1 and -C2 cell lines derived from TRAMP mice were maintained in DMEM supplemented with 5% FCS, 5% NuSerum (Collaborative Biomedical Products, Bedford, MA), 5 µg/ml insulin (Sigma Chemical Co.), and 0.01 nM dihydrotestosterone (Sigma Chemical Co.). All of the mouse tissues for RNA analysis were isolated from male C57BL/6 mice.

SSH. TRAMP-C1 cells and mouse tissues were homogenized in Trizol reagent (Life Technologies, Inc.) to isolate total RNA. Poly(A)⁺-RNA was purified from total RNA by using the Oligotex mRNA Mini and Midi kits of Quagen (Chatsworth, CA). SSH was performed with the PCR-Select cDNA Subtraction Kit (Clontech) according to the manufacturer's protocol. SSH-derived gene fragments were inserted into pCR2.1-TOPO by using a TOPO TA cloning kit (Invitrogen). Transformed *Escherichia coli* were subjected to blue/white and ampicillin screening. White colonies were picked and stored in 25% glycerol in 96-well plates. Plasmid DNA was prepared, sequenced, and searched for homology against public databases. Secondary protein structure prediction was performed by using the web tool PSORT IL.⁴

Northern Analysis. Nylon membranes with UV-fixed total RNA (5 or 20 µg/lane) from normal mouse tissues and TRAMP-C cells and mouse poly(A)⁺ Northern blot containing mRNA samples from 12 different tissues (OriGene) were hybridized with the [³²P]dCTP-labeled cDNA fragments. The cDNA probes used were 260-bp (nucleotide 34–293) *mSteap* and 424-bp (nucleotide 25–448) *mPscA* cDNA fragments. As an internal control, β-actin was used to hybridize all of blots.

RT-PCR. All of the RNA used for RT-PCR was treated with DNase. cDNA synthesis was performed by oligodeoxythymidylate priming. For RT-PCR amplification, the following primer pairs were used: 5'-GGTGGCT-GAAGCCGTACTAT and 5'-GGATGATATGATGGCAGCGAC for *mSteap*, 5'-TTCTCCTGCTGGCCACCTAC and 5'-GCAGCTCATCCCTCACAAT

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³ The abbreviations used are: PSA, prostate-specific antigen; *STEAP*, six-transmembrane epithelial antigen of the prostate; *PSCA*, prostate stem cell antigen; *PSMA*, prostate-specific membrane antigen; TRAMP, transgenic adenocarcinoma mouse prostate; SSH, suppression subtractive hybridization; *mPscA*, mouse *PSCA*; *mSteap*, mouse *STEAP*; *mPsmA*, mouse *PSMA*; poly(A), polyadenylate; RT-PCR, reverse transcription-PCR; RACE, rapid amplification of cDNA ends.

⁴ <http://psort.ims.u-tokyo.ac.jp/form2.html>.

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1 MEISDDVTFPEQLWKKMKFKGNLEDDSYSTKDSGETSMLKRPGLSHLQHAV mSteap
1 MESRKDIPTNQEELWKKMKERRNLEDDDLKDKTGETSMLKRPVLLHLHQTA STEAP
51 HYDAFDCPSELQHTQEPFFNWRLEPVKVAIISSILTFLYTLLEIITPLVTF
51 HADEPDCPSELQHTQELFPQWHLPEIKIARAIASLTFLYTLLEVIHPLAT
101 SREQYFYKIPILVINKVLPMAITLLALVYLPGLAAAVQLRHNGTKYKFF
101 SQQYFYKIPILVINKVLPMSVITLLALVYLPGVIAAIVQLRNGTKYKFF
151 FFWLDRMMLARKQFGLLSFFFAVLVAVYSLSYPMRRSYRYKLLNWAYKQV
151 FHWLDRMMLTRKQFGLLSFFFAVLVAVYSLSYPMRRSYRYKLLNWAYQVQ
201 QQNKEDAWVEHDVWRMEIYVSLGIVGLAIALALLAVTSIPSPVSDSLTWREF
201 QQNKEDAWIEHDVWRMEIYVSLGIVGLAIALALLAVTSIPSPVSDSLTWREF
251 HYIQSKLGIIVSLLGLTGHVHALVFAWKKWVDVSPQVWYMPPTFMIAVFLPTL
251 HYIQSKLGIIVSLLGLTIHALVFAWKKWIDIKQFVWYTPPTFMIAVFLPIV
301 VLTICKIALCLPCLRRKILKIRCGWEDVSKINRTEMASRL
301 VLLFKSIEFLPCLRRKILKIRHGWEDVTKINKTEICSQL

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Fig. 1. Amino acid sequences of *mSteap* and human *STEAP*. Shaded regions highlight conserved amino acids. The underlined regions correspond to the putative membrane-spanning domains. No NH₂-terminal signal peptide is found, and NH₂ and COOH termini are both predicted to be intracellular by use of web tool PSORT II.

for *mPscA*, and 5'-GGGAAGATTGTGATTGCCAGAT and 5'-GCCTC-CGTCCTTCTCTCTCA for *mPscA*. Thermal cycling was performed for 35 cycles at 94°C for 30 s, 58°C for 1 min, and 72°C for 1 min.

RACE. RACE reactions were performed to identify full-length *mSteap* and *mPscA* following the manufacturer's instructions by 5' and 3' RACE systems (Life Technologies, Inc.). Templates for RACE reactions were RNA isolated from TRAMP-C1 cells and mouse prostate tissues. 5'-RACE reactions were performed with the gene-specific primers 5'-GGATGATATGATGGCAGC-GAC and 5'-CCTGCGTGTGCTGAAGCTCG for *mSteap* and 5'-GTGGAGT-GCAGCTCATCCCTTCA and 5'-GCCCGGATGCGCGATGTAA for *mPscA*. The 3'-RACE reactions were conducted with the gene-specific primers 5'-CTCTCGCACTTGACAGCAGC for *mSteap* and 5'-GGGCCATGGACT-CGTGACAGT for *mPscA*.

Chromosomal Mapping. Chromosomal localization of *mSteap* and *mPscA* was determined by using the Mouse/Hamster Radiation Hybrid Panel (Research Genetics, Inc.). *mSteap* gene products were amplified by PCR with the following primers: 5'-CTCTCGCACTTGACAGCAGC and 5'-GGAT-GATATGATGGCAGCAGC. The primers used for mapping *mPscA* were 5'-GCACAGCACAGATGAACAACAG and 5'-GCACAGGTCAGAGTAG-CAGCAC. The resulting mapping vectors were processed through a mapping program.⁵

RESULTS

SSHs Identify *mSteap* and *mPscA*. In pursuit of genes that are up-regulated in prostate tumors in the TRAMP model, cDNA derived from mouse kidney and spleen was subtracted from cDNA isolated from TRAMP-C1 cells. Extensive screening was performed on a selected set of SSH-derived clones to look for genes that were differentially regulated between tester and driver cDNA. Among the differentially expressed clones, two gene fragments were highly homologous to human *STEAP* and *PSCA*, respectively. The full-length cDNA sequences of these two genes were amplified through 5' and 3' RACE reactions using RNA from TRAMP-C1 cells and normal prostate tissues as a template. Sequence analysis revealed that a novel 1175-bp cDNA, which did not show significant identity with any known mouse genes, shared 80% homology with human *STEAP* at both the nucleotide and amino acid levels and, therefore, represented the *mSteap* (accession no. AF 297098). Similar to human *STEAP*, *mSteap* also encodes a predicted 339 amino acid protein with six transmembrane domains without a signal peptide (Ref. 12; Fig. 1). Another novel 864-bp cDNA, which shares a 65% identity with human *PSCA* at both nucleotide and amino acid levels, is *mPscA* (accession no. AF 319173). Although the protein sequence of *mPscA* had been reported by Reiter *et al.* (9), the nucleotide sequence of *mPscA* could not be found in the public databases. *mPscA* additionally

shares 52% nucleotide and 33% amino acid homology with mouse stem cell antigen 2.

Expression of *mSteap* and *mPscA* Is Prostate-predominant. The distribution of *mPscA* and *mSteap* in normal mouse tissues was examined by Northern blot and RT-PCR analysis. Northern blotting of normal mouse prostate tissue RNA has showed that *mSteap* is ~1.2 kb (Fig. 2). Small amounts of *mSteap* mRNA could be detected in kidney and testis after prolonged exposure (3 days *versus* 1 day for prostate) in mouse poly(A)⁺ Northern blot containing mRNA samples from brain, heart, kidney, liver, lung, muscle, skin, small intestine, spleen, stomach, testis, and thymus (data not shown). The *mPscA* transcript in normal mouse prostate is ~0.9 kb (Fig. 2). *mPscA* is expressed predominantly in prostate, with a lower level of expression present in kidney, colon, and testis (data not shown). This distribution of *mPscA* is consistent with that reported by Reiter *et al.* (9). RT-PCR also confirmed the distribution pattern of *mSteap* and *mPscA* analyzed by the Northern blot analysis (Fig. 3). Together, these data indicate that *mSteap* and *mPscA* expression is largely prostate-specific.

***mSteap* and *mPscA* Are Highly Expressed in Primary and Metastatic Tumors of TRAMP Mice.** Human *STEAP* has been shown to be expressed in human primary tumors and cell lines derived from metastatic lesions of prostate cancers (12), and human *PSCA* is detected in both primary and metastatic lesions of human prostate cancers (9, 24). Here, we examined the expression of their mouse homologues in TRAMP-C cells and cancer tissues from TRAMP mice. Northern blot and RT-PCR analysis demonstrated that both *mSteap* and *mPscA* were expressed in TRAMP-C cells and prostate tumor tissues from TRAMP mice (Fig. 2 and Fig. 4). Furthermore, they were highly detected by RT-PCR in metastatic samples from lymph node, liver, and viscera of TRAMP mice (Fig. 4). Comparison of *mSteap* and *mPscA* expression in normal prostate, prostate tumors, and TRAMP-C cells suggested that *mSteap* and *mPscA* were up-regulated in TRAMP prostate tumors and TRAMP-C cells (Fig. 2). However, because the RNA samples derived from normal prostate tissues contain small amounts of message from other tissues nearby the prostate, the expression level of *mSteap* and *mPscA* in normal prostate might be underestimated.

***mPscA* Is Also Detected in Primary and Metastatic Tumors of TRAMP Mice.** On the basis of the expression of *mPscA* and *mSteap* in TRAMP prostate tumors, we inferred that some other human prostate-specific gene homologues might also be expressed in the TRAMP model. We selected *mPscA*, which was the only mouse prostate-specific gene we were able to find in GenBank databases

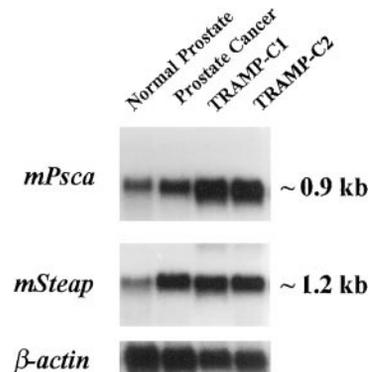


Fig. 2. Northern blot analysis of *mSteap* and *mPscA* expression. Total RNA from normal prostate, TRAMP prostate tumor tissues, TRAMP-C1 cells, and TRAMP-C2 cells were analyzed by using *mSteap*- or *mPscA*-specific probes. The normal prostate lane contained 20 μ g of total RNA, and the other lanes were prepared with 5 μ g of total RNA. All of the RNA samples were normalized by ethidium bromide staining and subsequent analysis with an β -actin probe.

⁵ http://www.genome.wi.mit.edu/cgi-bin/mouse_rh/rhmap-auto/rhmapper.cgi.

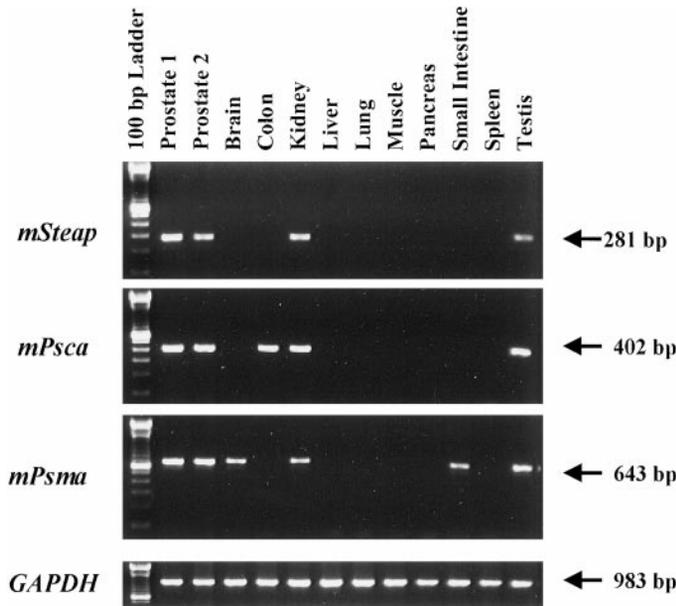


Fig. 3. RT-PCR analysis of mRNA expression of *mSteap*, *mPscA*, and *mPsmA* in normal mouse tissues. DNase-treated total RNA from the indicated tissues was submitted to 35 cycles of RT-PCR amplification with *mSteap*-, *mPscA*-, and *mPsmA*-specific primers, respectively. All of the PCR products were visualized on 2% agarose gel stained with ethidium bromide.

presently (accession no. AF026380). *mPsmA* shares 76% nucleotide and 86% amino acid homology with human PSMA (23). RT-PCR using the *mPsmA* specific primers showed that *mPsmA* was expressed in mouse brain, kidney, testis, and prostate tissues (Fig. 3). Similar to *mSteap* and *mPscA*, *mPsmA* is also highly detected in TRAMP-C cells, primary cancer tissues, and metastatic samples from lymph node, liver, and viscera of the TRAMP model (Fig. 4).

***mSteap* and *mPscA* Genes Localize to Chromosome 5.** Chromosomal mapping was performed by using radiation hybrid analysis. *mSteap* localized to Chr05, 20.33 cR from D5Mit331, a region corresponding to the location of human *STEAP* (7p22.3; Ref. 12) according to the human-mouse map at public databases.⁶ *mPscA* localized to Chr05, 24.08 cR from D5Mit89. This region did not exhibit a clear correlation with the chromosomal location of human *PSCA* (8q24.2; Ref. 9) in the human-mouse map. Because this human-mouse map is not presently completed, further development of this database may provide more information about this issue.

DISCUSSION

In search of novel genes preferentially expressed in the prostate tumors of TRAMP mice, we have isolated and characterized *mSteap* and *mPscA* using a subtraction approach. Of interest, human *STEAP* and *PSCA* were also identified by use of subtractive approaches in the LAPC-4 xenograft model of human prostate cancer (12, 9). *mSteap* and human *STEAP* share high homology at both the nucleotide and amino acid levels. The putative six-transmembrane domains are conserved in *mSteap* and human *STEAP*. This structure suggests a potential function as a channel, receptor, or transporter protein. Similarly, *mPscA* is highly homologous to human *PSCA* at both nucleotide and amino acid levels. Because of this homology, Reiter *et al.* (9) were able to identify the *mPscA* cDNA through searching the murine expressed sequence tag (EST) databases with the sequence of human *PSCA*. At present, the biological function of mouse and human *PSCA*

is not clear. According to its homology to Ly-6 families, *PSCA* is considered a member of Ly-6 family, which may be involved in signal transduction and cell-cell adhesion (9).

The expression profiles of *mSteap* and *mPscA* are similar to the largely prostate-specific expression of their human homologues. *STEAP* and *PSCA* belong to a small group of cell-surface antigens that are expressed in prostate cancer and represent potential targets for both antibody-based and T-cell-mediated therapies. This family includes *PSA* (1), *PAP* (2), *PTCA-1* (5), *PSGR* (20), *PSMA* (3), *STEAP* (12), and *PSCA* (9). Of this family, *PSMA*, *PTCA-1*, *PSA*, and *PAP* are secretory proteins that have been found in considerable concentrations in peripheral blood and, thus, represent somewhat less desirable targets for immunotherapy. In contrast, *STEAP* and *PSCA* are not secreted. Human *STEAP* and *PSCA* are further found to be stably expressed in advanced prostate cancer tissues, and *PSCA* expression is retained by metastatic tissues of prostate cancer (9, 12, 24). These proteins are potentially good targets for immunotherapy of prostate cancer. Similar to their human homologues, *mSteap* and *mPscA* are expressed in primary TRAMP prostate cancer tissues, TRAMP-C cell lines, and metastatic samples from lymph node, liver, and viscera of TRAMP mice.

Human *PSMA* is one of the best-characterized prostate-specific genes and the first prostate-specific gene used in clinical trials for the immunotherapy of prostate cancer (25, 26). Its mouse homologous gene, *mPsmA*, has been released recently from the GenBank database. *mPsmA* is highly homologous to human *PSMA* and maps to chromosome 7 (7D1-D2; Ref. 23). We have shown here that *mPsmA* is also expressed in primary prostate cancer and metastatic lesions of TRAMP mice. These results imply that other human prostate-specific and cancer-associated antigens may have their homologues in the TRAMP model, and hence this mouse model may prove particularly useful in evaluating the function of these gene products and therapeutic efficacy of treatments targeting these molecules.

Ideal targets for therapy of prostate cancer should be antigens that are exclusively expressed in nonvital tissues like prostate, highly expressed in metastatic disease, and accessible to therapeutic modalities. Unfortunately, the majority of defined prostate-specific gene products do not fulfill all of these conditions. Like human *STEAP*, *PSCA*, and *PSMA* we have discussed here, they are not exclusively

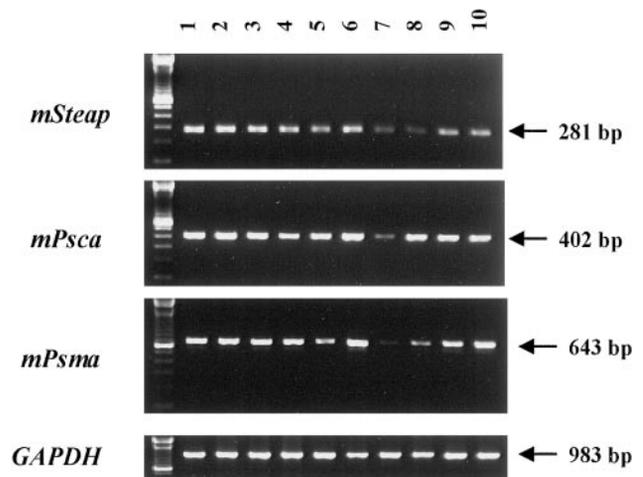


Fig. 4. RT-PCR analysis of mRNA expression of *mSteap*, *mPscA*, and *mPsmA* in TRAMP-C cells, primary tumors, and metastatic tumors of TRAMP mice. DNase-treated total RNA was submitted to 35 cycles of RT-PCR amplification with *mSteap*-, *mPscA*-, and *mPsmA*-specific primers, respectively. Lanes are: 1, TRAMP-C1; 2, TRAMP-C2; 3 and 4, primary prostate tumors; 5, 6, and 7, liver metastases; 8 and 9, lymph node metastases; and 10, visceral metastases. All of the PCR products were visualized on 2% agarose gel stained with ethidium bromide.

⁶ <http://www.ncbi.nlm.nih.gov/Homology>.

prostate-specific. Low-level human *STEAP* mRNA is detected in the colon and liver, and its protein is found in the bladder at moderate level. Small amounts of human *PSCA* mRNA are detected in kidney and small intestine, and human *PSMA* is expressed in various human tissues (27). Effective therapies against these targets may bear the risk of inducing damage to the normal organs expressing these antigens. Although no autoimmune disease has been observed in PSMA-based immunotherapies in clinical trials, these studies (25, 26) have not reported any consistent and effective immune responses generated against *PSMA*. Because *mSteap*, *mPscA*, and *mPsmA* are expressed in some normal tissues other than prostate, these murine antigens can be used to evaluate such therapeutic side effects. In the case of immunological approaches, the immune system may have ignored or developed tolerance to the prostate/cancer-specific genes because they are also expressed in normal prostate. Therefore, these murine prostate-specific antigens combined with the TRAMP model will provide a good model system to investigate various immunotherapeutic strategies to treat prostate cancer. In addition, these antigens are murine by nature. Studies with these antigens will be more representative *in vivo* than approaches using transfected xenogeneic antigens.

In summary, *mSteap*, *mPscA*, and *mPsmA* are homologous to their human counterparts, largely prostate-specific, and highly expressed in primary and metastatic cancers of TRAMP mice. These murine genes in combination with the TRAMP model will provide an animal system for the evaluation of prostate antigen-directed therapeutic strategies against prostate cancer.

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Murine Six-Transmembrane Epithelial Antigen of the Prostate, Prostate Stem Cell Antigen, and Prostate-specific Membrane Antigen: Prostate-specific Cell-Surface Antigens Highly Expressed in Prostate Cancer of Transgenic Adenocarcinoma Mouse Prostate Mice

Damu Yang, Gregory E. Holt, Markwin P. Velders, et al.

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