Progress in targeted therapy for prostate cancer via cell surface proteins (Review)

HUA LUO[1,2]

[1]Department of Urology, Deyang Hospital of Sichuan Provincial People's Hospital, Deyang, Sichuan 618000, P.R. China;
[2]Department of Urology, The Second People's Hospital of Deyang City, Deyang, Sichuan 618000, P.R. China

Received August 8, 2025; Accepted October 23, 2025

DOI: 10.3892/br.2025.2080

Abstract. Prostate cancer (PCa), particularly metastatic castration-resistant PCa, remains a significant therapeutic challenge. Cell-surface proteins have emerged as promising therapeutic targets. The present review examines the biological characteristics of PCa cell surface proteins focusing on major targets, such as prostate-specific membrane antigen, six-transmembrane epithelial antigen 1, trophoblast cell-surface antigen 2, and prostate stem cell antigen. These targets provide the foundation for the development of emerging therapeutic strategies, including radioligand therapy, antibody-drug conjugates, and bispecific T cells and chimeric antigen receptor T cell therapy. Combining the latest clinical trial data, the present review discusses the efficacy of targeted therapy, the mechanisms of drug therapy resistance, and combination treatment strategies, analyzing their potential application in the management of PCa and exploring prospects for the development of precision therapy in the future. Additionally, this review aims to systematically summarize the relevant progress in this field. In conclusion, the findings provide a theoretical basis and clinical guidance for molecular-targeted therapy in PCa, thereby promoting further research and applications.

Contents

1. Introduction
2. Clinical challenges and therapeutic differentiation in castration-resistant PCa
3. Biological characteristics and main targets of PCa cell surface proteins
4. Therapeutic strategies targeting surface proteins of PCa cells
5. Mechanisms and strategies of resistance to cell surface protein targeted therapy
6. Clinical application prospects
7. Challenges and future research directions
8. Conclusion

Correspondence to: Dr Hua Luo, Department of Urology, Deyang Hospital of Sichuan Provincial People's Hospital, 340, Section 1, Minjiang West Road, Jingyang, Deyang, Sichuan 618000, P.R. China
E-mail: 276806341@qq.com

Key words: prostate cancer, cell surface proteins, targeted therapy, prostate-specific membrane antigen

1. Introduction

Prostate cancer (PCa) is a leading cause of cancer-related deaths in men worldwide (1). As medical technology evolves, approaches for treating PCa are being regularly refined (2). Metastatic castration-resistant PCa (mCRPC) poses significant therapeutic challenge (3). Current treatment modalities, including hormone therapy, chemotherapy, and radiotherapy, show limited effectiveness against mCRPC and frequently cause considerable adverse effects (4). The progression of metastatic PCa is influenced by multiple factors such as tumor load, molecular traits, and resistance to therapies (5).

Proteins located on the cell surface serve as specific markers for tumors and are increasingly recognized as key targets for targeted therapies in PCa (6). Research indicates that proteins such as prostate-specific membrane antigen (PSMA) are significantly overexpressed in PCa cells, making them promising options for targeted treatment (7). These proteins play a role in tumor proliferation and spread, as well as in mechanisms that allow tumors to evade the immune system (8). Focusing on these surface proteins can enhance treatment efficacy and minimize adverse effects (9).

The shortcomings of conventional treatment strategies have led to the development of targeted therapies. Although chemotherapy and radiation therapy continue to play crucial roles in PCa management, their effectiveness is frequently hindered by variations within tumors and resistance to medications (10). Recently, therapies that focus on cell surface proteins have gained attention as innovative treatment options (11). This strategy not only targets particular cancer cells but also enhances the precision of drug delivery and increases the availability of medications in the body (12). Consequently, the management of mCRPC must differ from that of hormone-sensitive diseases (13,14), necessitating personalized strategies that target specific cell surface

markers [such as PSMA and six-transmembrane epithelial antigen 1 (STEAP1)] and often employ combination therapies to overcome resistance (15-17).

This review aims to comprehensively outline the advancements in targeted treatments associated with PCa cell surface proteins, focusing on the underlying molecular processes, therapeutic approaches, and their clinical relevance. By examining various strategies for targeted therapy and their implementation in clinical settings, it seeks to offer improved treatment alternatives for patients with PCa and inform future research pathways.

2. Clinical challenges and therapeutic differentiation in castration-resistant PCA

mCRPC represents a distinct and advanced stage of PCa characterized by disease progression despite androgen deprivation therapy (18). The management of mCRPC necessitates a differentiated approach compared to hormone-sensitive PCa due to its unique biological behavior, resistance mechanisms, and therapeutic vulnerabilities (19). Key challenges in mCRPC include persistent androgen receptor (AR) signaling, intratumoral heterogeneity, adaptive immune evasion, and the emergence of treatment-resistant clones (20).

Current standard therapies for mCRPC, including novel hormonal agents (such as enzalutamide and abiraterone), chemotherapies (for example docetaxel), and radiopharmaceuticals (such as ^{177}Lu-PSMA-617), have demonstrated survival benefits (21). However, their efficacy is often limited by primary or acquired resistance, which is driven by AR alterations, neuroendocrine differentiation, and an immunosuppressive tumor microenvironment (TME) (22).

Therapeutic differentiation in mCRPC involves several key approaches: i) Molecular stratification based on genomic alterations (for example BRCA1/2 and PTEN), AR variant expression, and PSMA avidity (23); ii) sequential and combination therapies that leverage synergistic effects between AR-directed agents, radioligands, immunotherapies, and targeted agents (24); and iii) liquid biopsy and biomarker monitoring utilizing circulating tumor cells (CTCs) and cell-free DNA to track clonal evolution and treatment response (25). Emerging evidence supports the integration of multi-omics profiling and artificial intelligence (AI) to guide personalized therapy in mCRPC, emphasizing the necessity for dynamic treatment adaptation in response to evolving tumor biology (26).

3. Biological characteristics and main targets of PCa cell surface proteins

PSMA. PSMA is a glycoprotein that spans the cell membrane and is predominantly found in PCa cells, especially in aggressive forms, such as metastatic, poorly differentiated, and castration-resistant variants, where its elevated presence often correlates with increased tumor severity (27). Although normal tissues, including parts of the urinary system and certain nerve tissues, exhibit lower PSMA levels, PSMA is markedly overexpressed on cancer cell surfaces (6). This overexpression plays a crucial role in tumor cell growth and survival within the TME, and possibly in promoting new blood vessel formation in tumors. The distinct expression pattern of PSMA, characterized by high levels in tumors and minimal expression in non-tumor tissues, makes it a promising therapeutic target (6). Treatment with radiopharmaceuticals, such as Lu-PSMA-617, can effectively destroy cancer cells while sparing healthy tissue (28). Additionally, PSMA is not exclusive to PCa cells; it is also present in some newly formed blood vessels associated with tumors (29). The use of radiolabeled compounds, such as 68Ga-PSMA-11, enhances the diagnostic precision for detecting metastatic cancer (30). However, PSMA expression shows intra-and intertumoral heterogeneity, which may lead to varying treatment responses (31). In addition, its low expression in normal tissues, such as the salivary glands and kidneys, may cause off-target toxicity, requiring close monitoring during treatment (32).

STEAP1. STEAP1 is frequently overexpressed in PCa, especially in advanced and metastatic forms, with >85% of prostate tumors exhibiting this expression (33). By contrast, normal tissues show minimal expression, highlighting their potential as significant targets for therapy (34). This is further supported by the link with biomarkers found in STEAP1-positive extracellular vesicles, which can assist in both diagnosis and prognosis (35). As a cell surface antigen, STEAP1 plays a role in various aspects of tumor development, including cell growth, migration, survival, intercellular communication, and metal metabolism (36). It also enhances tumor cell functions through pathways such as PI3K/Akt and is linked to aggressive characteristics such as invasion and metastasis (37). Previous research on PCa models have demonstrated that STEAP1 exerts antitumor effects when used in chimeric antigen receptor T (CAR-T) cell therapy (38). When combined with localized IL-12 therapy, it was shown to improve treatment effectiveness by modifying the TME and countering antigen escape (29). Moreover, clinical trials are being conducted using STEAP1-targeted T-cell inducers and antibody-drug conjugates (ADCs) (39). In summary, STEAP1 is a promising target in PCa; however, its expression dynamics in advanced cancer and association with metal metabolism need to be further elucidated.

Other key cell surface proteins. Additional important proteins on cell surfaces include trophoblast cell-surface antigen 2 (TROP-2), a transmembrane protein frequently found at elevated levels in various cancers, including PCa, making it a promising candidate for ADCs (40). Ongoing clinical trials are assessing the effectiveness of sacituzumab-govitecan in treating urothelial carcinoma and PCa, with supportive evidence of its anticancer properties emerging from animal studies (41). Likewise, prostate stem cell antigen (PSCA) is present in ~90% of PCa cases and is associated with tumor aggressiveness, leading to the development of targeted immunotherapies such as CAR-T cells and ADCs (42). Nonetheless, obstacles such as the immunosuppressive nature of the TME, potential off-target effects, and variability in expression levels may pose challenges (43). Furthermore, delta-like ligand 3 (DLL3) is overexpressed in neuroendocrine PCa (NEPC), linking it to tumor severity and patient prognosis (44). Monoclonal antibodies and radioimmunotherapy, including 177Lu-labeled antibodies, have demonstrated preclinical promise. However,

Table I. Summary of major cell surface protein targets in prostate cancer and their characteristics.

Target	Expression profile	Primary functions	Therapeutic modalities	Development stage/ challenges
PSMA	Highly expressed in mCRPC, high-grade tumors, and tumor neovasculature; low-level expression in salivary glands and kidneys (18,19,21)	Cell growth, survival, TME adaptation, and a potential role in angiogenesis (18,19,21)	RLT (such as 177Lu-PSMA-617), ADCs, BiTEs, and CAR-T (20,39,45,48,52)	Standard of care (mCRPC); challenges: Expression heterogeneity, off-target toxicity, drug resistance (23,24,106)
STEAP1	Overexpressed in >85% of PCa, especially in advanced/ metastatic disease; minimal expression in normal tissues (25)	Cell proliferation, migration, intercellular communication, and metal ion metabolism (6,28)	CAR-T, ADCs, and BiTEs (29,30,51)	Under clinical investigation; challenges: Expression dynamics in advanced cancer, role in metal metabolism (6,25)
TROP-2	Highly expressed in various carcinomas (including mCRPC), and associated with poor prognosis (31)	Calcium signaling, cell proliferation, migration, and adhesion (31)	ADCs (such as sacituzumab govitecan) (31,32)	Clinically validated (ADCs); less explored in other modalities (such as CAR-T) (31)
PSCA	Upregulated in ~90% of PCa cases, and associated with tumor aggressiveness (33)	Cell proliferation, invasion, and stem cell-like properties (33)	CAR-T, and ADCs (33)	Preclinical/early clinical; challenges: Immunosuppressive TME, and off-target potential (33,34)
DLL3	Specifically overexpressed in NEPC (35)	Ligand for Notch signaling pathway, and involved in cell fate determination (35)	Radioimmunotherapy, and monoclonal antibodies (35,36)	Preclinical/early clinical; challenges: Expression in non-neuroendocrine tumors and patient variability (35)
CELSR3	Highly expressed in NEPC (37)	Regulates cell polarity and migration via the Wnt/PCP pathway (37)	CAR-T and ADCs (exploratory) (37)	Emerging target (preclinical); requires more functional studies and clinical validation (37)
GPC3	Upregulated in CRPC (38)	Promotes tumor growth by regulating the Hedgehog signaling pathway (38)	ADCs (exploratory) (39,103)	Emerging target (preclinical); ADC trials in liver cancer inform PCa potential (38,103)

PSMA, prostate-specific membrane antigen; CRPC, castration-resistant prostate cancer; STEAP1, six-transmembrane epithelial antigen of the prostate 1; TROP-2, trophoblast cell-surface antigen 2; PSCA, prostate stem cell antigen; DLL3, delta-like ligand 3; CELSR3, cadherin EGF LAG seven-pass G-type receptor 3; GPC3, glypican-3; TME, tumor microenvironment; mCRPC, metastatic castration-resistant prostate cancer; NEPC, neuroendocrine prostate cancer; RLT, radioligand therapy; ADCs, antibody-drug conjugates; BiTEs, bispecific t-cell engagers; CAR-T, chimeric antigen receptor t-cell therapy; PCa, prostate cancer.

concerns regarding their expression in non-neuroendocrine tumors and patient variability must be resolved (45). In addition, emerging targets, such as cadherin EGF LAG seven-pass G-type receptor 3 (CELSR3) and glypican-3 (GPC3), have also attracted attention. CELSR3 is highly expressed in NEPC and is involved in the regulation of cell polarity and migration through the Wnt/PCP signaling pathway; its overexpression is associated with tumor invasiveness. Research has explored its potential as a target for CAR-T cells and ADC (46). GPC3 is upregulated in castration-resistant PCa and promotes tumor growth by regulating the Hh signaling pathway. Preclinical studies have shown that GPC3-targeting antibodies can inhibit tumor progression, and phase I clinical trials are underway (47) (Table I).

4. Therapeutic strategies targeting surface proteins of PCa cells

Radionuclide treatment. The drug 177Lu-PSMA-617 is a radioligand used for mCRPC that targets PSMA to deliver the radioactive isotope 177Lu directly to cancer cells, leading to their destruction (48). Findings from the VISION trial indicated that it notably enhanced both overall survival and quality of life in patients, and its favorable tolerability has established it as a standard treatment for mCRPC (49). Currently, there is growing interest in exploring novel radioactive isotopes, such as 161Tb-PSMA, which may offer promising avenues for combination therapies (50). Clinical studies have demonstrated the safety and effectiveness of 161Tb-PSMA, suggesting that

its use along with 177Lu-PSMA-617 could potentially amplify therapeutic outcomes (51). Overall, radioligand therapy (RLT), such as 177Lu-PSMA-617, has been demonstrated to significantly improve survival in patients with mCRPC; however, drug resistance and heterogeneous expression remain major challenges.

ADCs. ADCs are designed to transport cytotoxic medications directly to cancer cells using antibodies that specifically attach to tumor antigens (52). This targeted approach enhances the therapeutic effectiveness while minimizing harm to healthy tissues (53). PSMA is recognized as a well-established therapeutic target that facilitates efficient delivery of ADCs. Clinical studies have indicated favorable results and manageable side effects in patients with mCRPC, including a 50% or more reduction in prostate-specific antigen levels during second-line treatments, along with some instances of complete responses (54). Additionally, TROP-2, which is prominently expressed in metastatic PCa and linked to poor prognosis, represents another significant target for ADCs, showing encouraging clinical results (40). In contrast to conventional chemotherapy, the targeted nature of ADCs mitigates widespread toxicity and drug resistance (55). ADCs achieve precise delivery; however, the internalization efficiency of the target, linker stability, and off-target toxicity limit their widespread applications.

Bispecific T-cell engagers (BiTEs). BiTEs are designed to bind both tumor-specific antigens and CD3 receptors on T cells, thereby effectively linking T cells to cancer cells (56). This connection not only activates T cells to kill tumor cells but also facilitates the direct destruction of the tumor. For instance, AMG 160, which targets PSMA, elicits cytotoxic effects in PCa, whereas BiTEs that target STEAP1 further improve therapeutic outcomes (57). In addition to their direct effects on tumors, BiTEs enhance the immune response against cancer by promoting the release of cytokines from activated T cells, which, in turn, activate nearby immune cells (58). Although the combination of BiTEs with immune checkpoint inhibitors has the potential to address the immunosuppressive environments found in 'cold tumors', such as PCa, their application in clinical settings is hindered by issues such as cytokine release syndrome (CRS) and other immune-related adverse effects (irAEs) (59). BiTEs activate T cells with strong cytotoxic effects; however, CRS and neurotoxicity limit their clinical application.

CAR-T cell therapy. CAR-T cell therapy is a groundbreaking immunotherapeutic approach. Preclinical research has demonstrated that CAR-T cells targeting the STEAP1 antigen in PCa cells can effectively identify and eliminate tumor cells (60). Additionally, CAR-T therapy targeting PSMA has been proven effective in patients with metastatic disease. Studies conducted *in vitro* and in animal models revealed enhanced anti-tumor properties, particularly when combined with chemotherapy agents (60,61). Nonetheless, obstacles, such as the immunosuppressive nature of the TME and the mechanisms of antigen escape, hinder their overall effectiveness, leading to the exploration of dual CAR-T cells paired with IL-23 antibodies to enhance their proliferation and functionality (62). NEPC is a particularly aggressive variant that poses distinct treatment challenges owing to the presence of specific antigens. CAR-T cells targeting carcinoembryonic antigen-related cell adhesion molecule 5 have shown significant cytotoxic potential in preclinical studies, thereby addressing some of the shortcomings of traditional therapies (63). Although CAR-T has made breakthroughs in hematologic tumors, its efficacy is limited in solid tumors such as PCa, mainly due to: i) Immunosuppressive cells [such as myeloid-derived suppressor cells (MDSCs)] and factors (such as TGF-β) in the TME inhibiting T-cell function (64); ii) physical barriers such as fibrotic stroma hindering T-cell infiltration (65); and iii) antigen heterogeneity leading to antigen escape (66). By contrast, hematological tumors often exhibit more uniform antigen expression and a less immunosuppressive microenvironment, which facilitates the efficacy of CAR-T therapy (67). CAR-T cells exhibit potential in PCa, however the obstacles presented by the solid TME and antigen escape limit their efficacy, requiring combined strategies to overcome this bottleneck.

Comparison of BiTEs and CAR-T therapy. BiTEs and CAR-T cells are both T cell-directed therapies; however, each has advantages and disadvantages. BiTEs are easy to prepare, act quickly, and can be easily combined with immune checkpoint inhibitors (57); however, they have a short half-life and require continuous infusion, and the risk of CRS is high (59). Although CAR-T is durable and can expand *in vivo*, it is complex to prepare, costly, and easily inhibited by the TME in solid tumors (62,65). In summary, BiTEs offer a cost-effective, rapid response option for short-term intervention, whereas CAR-T therapy provides durable, personalized control, but faces manufacturing and TME challenges in PCa. The choice should be guided by treatment goals and patient-specific factors.

Nanotechnology and targeted delivery mechanisms. The use of nanoparticle-based drug delivery systems, which include functionalized nanoparticles, such as gold and polymeric carriers, allows for the precise targeting of cancer cells that express PSMA (68). This approach significantly improves drug bioavailability and can decrease systemic toxicity by 50-70% (68). These systems enhance the solubility and circulation duration of drugs, encourage tumor-specific accumulation to enhance effectiveness, and minimize side effects, while enabling treatment response monitoring through imaging methods (69). Furthermore, ultrasound-responsive nanocarriers are effective in delivering small interfering RNA to suppress gene expression in PCa cells (70). Nonetheless, the transition to clinical applications encounters obstacles, such as biocompatibility, immune reactions, and mechanisms of drug resistance. Nanocarriers enhance drug targeting and bioavailability; however, biocompatibility, immunogenicity, and large-scale production are challenges for translation.

Different treatment strategies have distinct advantages and disadvantages. RLT (such as 177Lu-PSMA-617) has a high response rate in PSMA-high-expressing mCRPC but may cause myelosuppression (71); ADCs have strong targeting but carry the risk of off-target toxicity (72); BiTEs activate T cells rapidly but can easily lead to cytokine release syndrome (73); and CAR-T therapy has been successful in

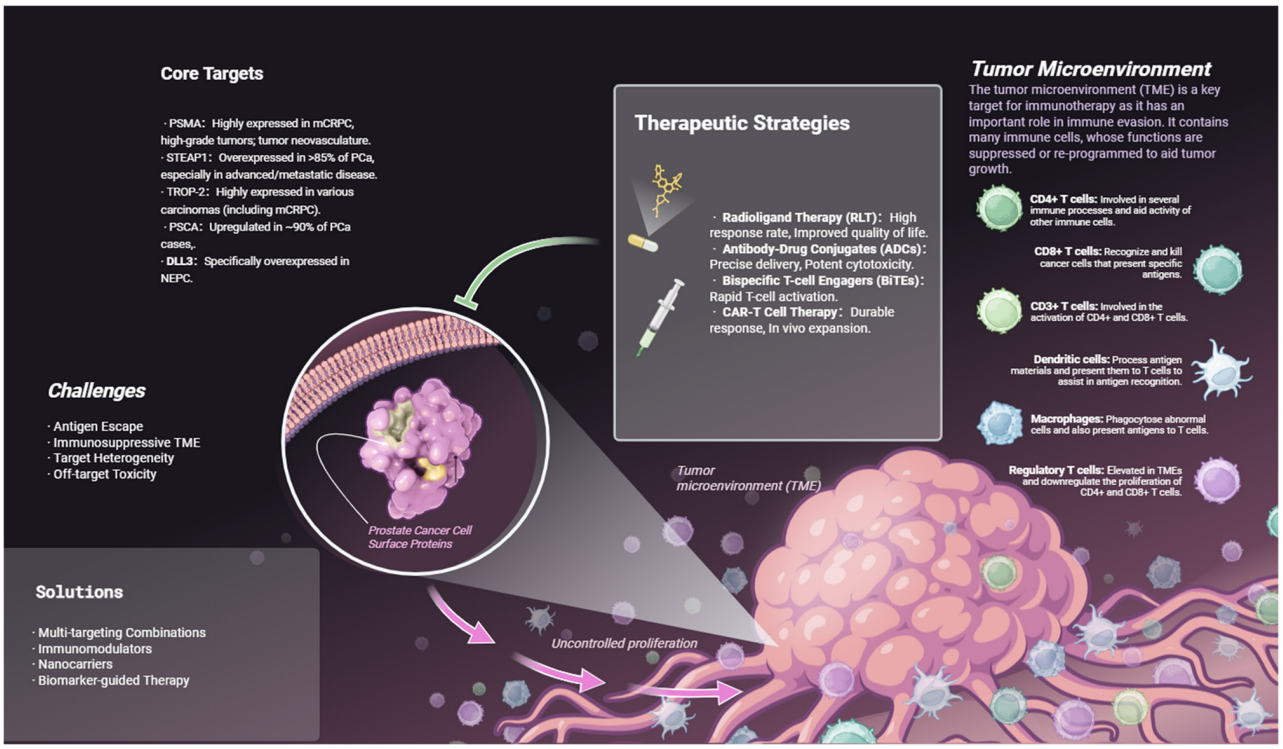

Figure 1. Therapeutic strategies targeting prostate cancer cell surface proteins and associated challenges. Schematic overview of key cell surface targets in prostate cancer (such as PSMA, STEAP1, TROP-2) and the corresponding therapeutic strategies, including RLT, ADCs, BiTEs, and CAR-T cell therapy. Major challenges such as antigen escape and an immunosuppressive microenvironment are highlighted, along with potential solutions including multi-targeting approaches and immunomodulation. PSMA, prostate-specific membrane antigen; STEAP1, six-transmembrane epithelial antigen of prostate 1; TROP-2, trophoblast cell-surface antigen 2; RLT, radioligand therapy; ADCs, antibody-drug conjugates; BiTEs, bispecific T-cell engagers; CAR-T, chimeric antigen receptor T-cell therapy; PSCA, prostate stem cell antigen; DLL3, delta-like ligand 3; TME, tumor microenvironment.

hematologic neoplasms but is limited in solid tumors such as PCa owing to TME suppression, resulting in limited efficacy (74). Longitudinal comparisons showed that both BiTEs and CAR-T cells are T cell-directed therapies, but BiTEs are cost-effective, quick to deploy, and suitable for short-term interventions, while CAR-T modifications are durable but complex to manufacture, making them more suitable for individualized long-term treatment (75) (Fig. 1).

5. Mechanisms and strategies of resistance to cell surface protein targeted therapy

Downregulation of antigen expression and antigen escape. The reduction in antigen expression and the phenomenon of antigen escape are significant factors in how tumor cells avoid detection by the immune system (76). This downregulation is often associated with various strategies employed by tumor cells to elicit immune responses. In PCa cells, the levels of PSMA and similar antigens frequently decrease due to factors such as genetic alterations, epigenetic modifications, and the effects of the TME (77). Lower PSMA expression can lead to a diminished response to immunotherapy, allowing tumor cells to evade immune monitoring (78). Furthermore, decreased antigen expression can hinder T-cell activation, thus impairing the overall immune response (79). Research indicates that antigen escape is intricately linked to the heterogeneity of tumor cells, where variations in antigen expression among different tumor cells contribute to the complexity and variability of immune responses against tumors (80). To cope with antigen downregulation, multitarget CAR-T cells (such as PSMA and STEAP1) or combined epigenetic regulators (such as HDAC inhibitors) can be used to stabilize antigen expression (81,82).

The diversity of PCa tumors significantly contributes to their ability to evade the immune system (83). Within PCa, various tumor cell subtypes may exhibit resistance to immunotherapy, whereas others respond positively to such treatments (84). This variability leads to differences in antigen expression, enabling some tumor cells to avoid immune detection by reducing or completely losing expression of crucial antigens (85). Additionally, elements within the TME that inhibit immune function, including tumor-associated macrophages and MDSCs, further facilitate the immune evasion of these tumor cells, intensifying the heterogeneity of the tumors (86-88). Consequently, investigating combination therapies aimed at enhancing immune responses and improving treatment effectiveness against tumors is critically important (89).

Regulation of the immunosuppressive microenvironment. Management of the immunosuppressive tumor environment is a crucial focus in PCa research. Factors associated with tumor-induced immunosuppression, such as S100A4, play a significant role in the initiation and progression of PCa (90). This protein is elevated in numerous tumors and is associated with unfavorable outcomes in patients with PCa (91). The

use of anti-S100A4 antibodies could potentially counteract this immunosuppressive effect in PCa, leading to improved treatment responses (92). Targeting S100A4 with anti-S100A4 antibodies may effectively reverse the immunosuppressive state of PCa, thereby improving patient response rates to treatment (90). The combination of immunomodulatory approaches and targeted therapies has great potential. For example, YY001, a novel EP4 antagonist, is vital for shaping the immune landscape of PCa (93). Research indicates that YY001 can reduce the differentiation and activity of MDSCs, while promoting T-cell growth and antitumor functions (93). By modulating cytokine and chemokine levels, YY001 can effectively restore a more favorable immune environment within tumors, functioning synergistically with anti-PD-1 antibodies to significantly enhance antitumor immune activity (93). The effectiveness of this combined approach highlights the potential of integrating immunomodulatory and targeted therapies for PCa treatment.

Therapeutic approaches in combination. To manage PCa, a dual-target strategy is employed in combination therapies (94). For instance, the AR blocker enzalutamide, which also targets PSMA, has been shown to enhance anticancer efficacy and improve survival rates during the emergence of drug resistance (95). In patients with mCRPC, 177Lu-PSMA-617 was associated with improved survival outcomes. Furthermore, integrating RLT with immune checkpoint inhibitors such as PD-1/PD-L1 antibodies or cytokine treatments can stimulate tumor-infiltrating lymphocytes and enhance the TME, thereby improving immune responses (96). The timing and dosage of the combination therapies can be fine-tuned (97). For example, the enzalutamide-docetaxel combination influences E2F transcription factor 1 (E2F1) expression, while synchronizing Janus kinase/signal transducer and activator of transcription with phosphoinositide 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR) inhibitors reveals synthetic lethality during epithelial-mesenchymal transition (98). The mechanisms of drug resistance, such as mutations in AR and epigenetic alterations, can be addressed by targeting pathways related to E2F1 or Snail, including XPO1/PI3K/mTOR (99). The combination of poly (ADP-ribose) polymerase (PARP) inhibitors and AR antagonists is effective against certain genetic mutations (100). In summary, multi-targeting approaches incorporate innovative drugs, including small molecules and ADCs, to improve tumor targeting while reducing toxicity. In conclusion, overcoming PCa resistance requires a multifaceted approach that addresses antigen loss, remodels the TME, and blocks compensatory pathways. Future efforts should prioritize the development of dynamic biomarker monitoring and rational, multi-targeted combination regimens.

6. Clinical application prospects

Tailored therapies based on biomarker insights. The combination and evaluation of multi-omics information, including genomics, transcriptomics, and proteomics, have enabled the discovery of novel biomarkers and treatment targets for PCa (101). Notably, mutations in genes such as BRCA1/2 are significantly linked to patient outcomes. Treatments targeting these mutations, such as PARP, have demonstrated efficacy (102). Molecular subtyping allows for the identification of high-risk patients and enhances the likelihood of successful treatment outcomes. Advanced AI techniques, such as deep and machine learning, aid in the accurate analysis of biomarkers and refinement of personalized treatment strategies (103). In addition, tracking CTCs is essential. The number of CTCs and the expression of surface proteins (such as PSMA and STEAP1) can indicate tumor severity, prognosis, and response to therapy (104), whereas liquid biopsy methods can efficiently isolate CTCs for ongoing clinical assessment (105). The management of mCRPC should be individualized based on several key factors, including i) tumor burden and metastatic sites; ii) expression levels of cell surface targets (such as PSMA PET/CT standardized uptake value); iii) genome characteristics (such as DNA repair defects); and iv) prior treatment history (106-108). Studies have shown that PSMA-targeted therapy can achieve a response rate of 60-70% in patients with mCRPC and high PSMA expression, while the effect is limited in patients with low expression, emphasizing the importance of target assessment before treatment (109-111).

Novel therapeutic targets are emerging in the field. Investigation of innovative surface proteins, including CELSR3, which is notably overexpressed in NEPC, is crucial for controlling cell growth and movement (46). Additionally, GPC3, which is linked to tumor aggressiveness, opens up new possibilities for the targeted treatment of PCa. CAR-T cells targeting CELSR3 have demonstrated significant tumor-suppressive activity in patient-derived xenograft models (37), while GPC3-targeted ADCs showed promising results in phase I trials for liver cancer, and its trial for PCa has been initiated (112). Concurrently, gene therapy-utilizing carriers, such as poly(lactic-co-glycolic acid) (PLGA) nanoparticles, can effectively transport nucleic acid medications aimed at PSMA (47). Treatment efficacy can be enhanced by employing a multifaceted approach that influences tumor dynamics and encourages immune cell infiltration (113). Advances in nanotechnology have enabled the development of immunotherapies. Functionalized nanoparticles can transport immunomodulatory agents and checkpoint inhibitors directly to tumor locations, enhancing biodistribution and facilitating synergistic combination therapies through the simultaneous delivery of various therapeutic compounds (114). Multi-omics and AI technologies drive individualized therapy; however, target validation, biomarker standardization, and clinical trial design remain key to achieving precision medicine.

7. Challenges and future research directions

Challenges related to specificity and safety in target selection. In the context of targeted therapy for PCa, a major challenge in choosing PSMA is the heterogeneity of the targets (115). Differences in PSMA expression across various tumor types and their microenvironments result in notable variations in treatment effectiveness among individuals (116). To address this heterogeneity, multimodal imaging (such as PSMA-PET/MRI) can be used to assess target expression and develop bispecific antibodies that simultaneously target both PSMA and STEAP1. Beyond this heterogeneity, there is the potential for unintended toxicity that can harm non-target tissues (117). This issue can be mitigated by the use

of functionalized nanoparticles and targeted ligands, which improve the precision of therapeutic agents (118). By utilizing tumor-targeting peptides in conjunction with nanoparticles, selective absorption of cancer drugs can be achieved, whereas biocompatible carriers help minimize systemic toxicity and ensure accurate delivery to PCa cells (119).

Addressing immune-related side effects. Immunotherapy can result in a range of irAEs when treating PCa and other urological malignancies, including mild symptoms such as rashes and fatigue as well as serious conditions such as endocrine dysfunction and potentially fatal pneumonia (120). Consequently, it is crucial to promptly recognize these issues through consistent monitoring of symptoms and patient feedback (121). Management approaches involve providing symptomatic relief for less severe cases and administering immunosuppressive medications, including steroids, to patients with moderate-to-severe irAEs, alongside patient education (122,123). Similarly, CAR-T cell therapy demonstrates promising effectiveness but requires rigorous safety oversight to monitor adverse reactions such as CRS and neurotoxicity (124). This requires ongoing evaluation of vital signs and neurological health, offering symptomatic care and tocilizumab when appropriate and a thorough pretreatment assessment to identify risk factors (125). In future, priority should be given to exploring the dynamic expression patterns of targets, the mechanisms of immunotoxicity, and the establishment of predictive models to optimize the treatment window.

8. Conclusion

Advancements in targeted therapies for PCa cell surface proteins, including PSMA, STEAP1, and TROP-2, have significantly improved the management of mCRPC. Innovative approaches such as RLT (including 177Lu-PSMA-617), ADCs, bispecific antibodies, and CAR-T cell therapy have demonstrated promising results. Nonetheless, challenges, such as antigen escape, immunosuppressive environments, and drug resistance, persist. Addressing these issues requires the development of combination therapies, including targeted drug pairings and the integration of RLT with immunotherapy, alongside personalized treatments informed by biological markers, such as genomic characteristics and CTC analysis. Future research should focus on the following directions: i) Elucidating the molecular mechanisms of antigen escape, particularly the roles of epigenetic regulation and TME-mediated immune suppression. ii) Prioritizing the clinical evaluation of combination strategies, such as RLT (for example 177Lu-PSMA-617) and immune checkpoint inhibitors (including anti-PD-1). iii) Accelerating the translational development of therapies against emerging targets (such as CELSR3- and GPC3-directed ADCs or CAR-T cells). iv) Developing integrated biomarker panels (for example combining ctDNA, CTCs, and radiomics) and standardizing toxicity management guidelines to improve patient quality of life. By fostering interdisciplinary collaboration to expedite the clinical application of novel therapies, targeted PCa treatment can advance to a more precise and effective era.

Acknowledgements

Not applicable.

Funding

The present review was funded by the Medical Research Project of Sichuan Medical Association (grant no. S2024047).

Availability of data and materials

Not applicable.

Authors' contributions

HL conceived and designed the review, drafted the manuscript, as well as read and approved the final mansucript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

References

1. Pullen RL Jr and Holter V: Nursing management of a patient with prostate cancer. Nursing 55: 25-35, 2025.
2. Campodonico F, Ennas M, Zanardi S, Zigoura E, Piccardo A, Foppiani L, Schiavone C, Squillace L, Benelli A, De Censi A, *et al*: Management of prostate cancer with systemic therapy: A prostate cancer unit perspective. Curr Cancer Drug Targets 21: 107-116, 2021.
3. Henriques V, Wenzel M, Demes MC and Köllermann J: Metastatic castration-resistant prostate cancer. Pathologe 42: 431-441, 2021 (In German).
4. Heck MM, Tauber R, Schwaiger S, Retz M, D'Alessandria C, Maurer T, Gafita A, Wester H, Gschwend JE, Weber WA, *et al*: Treatment outcome, toxicity, and predictive factors for radioligand therapy with 177Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. Eur Urol 75: 920-926, 2019.
5. von Amsberg G, Busenbender T, Coym A, Kaune M, Strewinsky N, Ekrutt J, Tilki D and Dyshlovoy S: Management of metastatic prostate cancer. Oncol Res Treat 8: 1-12, 2025.
6. Nezir AE, Khalily MP, Gulyuz S, Ozcubukcu S, Küçükgüzel SG, Yilmaz O and Telci D: Synthesis and evaluation of tumor-homing peptides for targeting prostate cancer. Amino Acids 53: 645-652, 2021.
7. Kumar BV, Sachan R, Garad P, Srivastava N, Saraf SA and Meher N: Dual targeting of prostate-specific membrane antigen and fibroblast activation protein: Bridging prostate cancer theranostics with precision. ACS Appl Bio Mater 8: 962-979, 2025.
8. Liu C, Chen S, Zhang Y, Zhou X, Wang H, Wang Q and Lan X: Mechanisms of Rho GTPases in regulating tumor proliferation, migration and invasion. Cytokine Growth Factor Rev 80: 168-174, 2024.
9. Wang J, Zhu J, Meng J, Qiu T, Wang W, Wang R and Liu J: Baicalin inhibits biofilm formation by influencing primary adhesion and aggregation phases in *Staphylococcus saprophyticus*. Vet Microbiol 262: 109242, 2021.

10. Du X, Zhang Y, Jia Y and Gao B: The Development of Al18F-NOTA-FAP-2286 as an FAP-Targeted PET tracer and the translational application in the diagnosis of acquired drug resistance in progressive prostate cancer. Pharmaceutics 17: 552, 2025.
11. Grewal K, Dorff TB, Mukhida SS, Agarwal N and Hahn AW: Advances in targeted therapy for metastatic prostate cancer. Curr Treat Options Oncol 26: 465-475, 2025.
12. Zhao Q, Mo Z, Zeng L, Yuan Y, Wang Y and Wang Y: Construction and evaluation of hepatic targeted drug delivery system with hydroxycamptothecin in stem cell-derived exosomes. Molecules 29: 5174, 2024.
13. Fan L, Gong Y, He Y, Gao W, Dong X, Dong B, Zhu HH and Xue W: TRIM59 is suppressed by androgen receptor and acts to promote lineage plasticity and treatment-induced neuroendocrine differentiation in prostate cancer. Oncogene 42: 559-571, 2023.
14. Archer M, Lin KM, Kolanukuduru KP, Zhang J, Ben-David R, Kotula L and Kyprianou N: Impact of cell plasticity on prostate tumor heterogeneity and therapeutic response. Am J Clin Exp Urol 12: 331-351, 2024.
15. Abida W, Beltran H and Raychaudhuri R: State of the Art: Personalizing treatment for patients with metastatic castration-resistant prostate cancer. Am Soc Clin Oncol Educ Book 245: e473636, 2025.
16. Xu J, Ma Y, Hu P, Yao J, Chen H and Ma Q: Recent advances in antibody-drug conjugates for metastatic castration-resistant prostate cancer. Zhejiang Da Xue Xue Bao Yi Xue Ban 54: 685-693, 2025 (In Chinese).
17. Mulati Y, Shen Q, Tian Y, Chen Y, Yao K, Yu W, Cui Y, Shi X, He Z, Zhang Q and Fan Y: Characterizing PSMA heterogeneity in prostate cancer and identifying clinically actionable tumor associated antigens in PSMA negative cases. Sci Rep 15: 23902, 2025.
18. Horak J, Petrausch U and Omlin A: Metastatic castration-resistant prostate cancer-what are rational sequential treatment options? Urologie 62: 1295-1301, 2023 (In German).
19. Davis ID: Combination therapy in metastatic hormone-sensitive prostate cancer: Is three a crowd? Ther Adv Med Oncol 14: 17588359221086827, 2022.
20. Reichert ZR and Hussain M: Androgen receptor and beyond, targeting androgen signaling in castration-resistant prostate cancer. Cancer J 22: 326-329, 2016.
21. Li PY, Lu YH and Chen CY: Comparative effectiveness of abiraterone and enzalutamide in patients with metastatic castration-resistant prostate cancer in Taiwan. Front Oncol 12: 822375, 2022.
22. Blanc C, Moktefi A, Jolly A, de la Grange P, Gay D, Nicolaiew N, Semprez F, Maillé P, Soyeux P, Firlej V, *et al*: The Neuropilin-1/PKC axis promotes neuroendocrine differentiation and drug resistance of prostate cancer. Br J Cancer 128: 918-927, 2023.
23. Russnes HG, Lingjærde OC, Børresen-Dale AL and Caldas C: Breast cancer molecular stratification: From intrinsic subtypes to integrative clusters. Am J Pathol 187: 2152-2162, 2017.
24. Saeed F, Berchuck JE, Bilen MA, Gandhi JS, Nazha B, Brown JT, Schuster DM, Jani AB, Yu J and Harik LR: Optimizing treatment for metastatic castration-resistant prostate cancer: Food and Drug Administration-approved therapies, emerging strategies, and biomarker-driven approaches. Cancer 131: e70037, 2025.
25. Hollanda CN, Gualberto ACM, Motoyama AB and Pittella-Silva F: Advancing leukemia management through liquid biopsy: Insights into biomarkers and clinical utility. Cancers (Basel) 17: 1438, 2025.
26. Liu HH, Tsai YS, Lai CL, Tang CH, Lai CH, Wu HC, Hsieh JT and Yang CR: Evolving personalized therapy for castration-resistant prostate cancer. Biomedicine (Taipei) 4: 2, 2014.
27. Adnan A and Basu S: PSMA Receptor-Based PET-CT: The basics and current status in clinical and research applications. Diagnostics (Basel) 13: 158, 2023.
28. Ramnaraign B and Sartor O: PSMA-targeted radiopharmaceuticals in prostate cancer: Current data and new trials. Oncologist 28: 392-401, 2023.
29. Rowe SP, Gorin MA and Pomper MG: Imaging of prostate-specific membrane antigen with small-molecule PET radiotracers: From the bench to advanced clinical applications. Annu Rev Med 70: 461-477, 2019.
30. Ali H, Rashid Ul Amin S, Hai A and Nizar N: Bony lesion analysis in carcinoma prostate: Methylene diphosphonate bone scan vs. Gallium-68 psma-11 pet/ct. J Ayub Med Coll Abbottabad 35: 415-418, 2023.
31. Zhang M, Li Y, Quan Z, Zhou X, Meng X, Ye J, Wang Y, Wang J, Qin W, Wang J and Kang F: Value of [68Ga] Ga-PSMA-11 PET/CT in reflecting the intra- and intertumor heterogeneity of neovascularization in clear cell renal cell carcinoma. Mol Pharm 22: 1529-1538, 2025.
32. Alaskarov A, Barel S, Bakavayev S, Kahn J and Israelson A: MIF homolog d-dopachrome tautomerase (D-DT/MIF-2) does not inhibit accumulation and toxicity of misfolded SOD1. Sci Rep 12: 9570, 2022.
33. Ihlaseh-Catalano SM, Drigo SA, de Jesus CM, Domingues MA, Trindade Filho JC, de Camargo JL and Rogatto SR: STEAP1 protein overexpression is an independent marker for biochemical recurrence in prostate carcinoma. Histopathology 63: 678-685, 2013.
34. Uemura H, Nakagawa Y, Yoshida K, Saga S, Yoshikawa K, Hirao Y and Oosterwijk Y: MN/CA I X/G250 as a potential target for immunotherapy of renal cell carcinomas. Br J Cancer 81: 741-746, 1999.
35. Khanna K, Salmond N, Lynn KS, Leong HS and Williams KC: Clinical significance of STEAP1 extracellular vesicles in prostate cancer. Prostate Cancer Prostatic Dis 24: 802-811, 2021.
36. Oosterheert W and Gros P: Cryo-electron microscopy structure and potential enzymatic function of human six-transmembrane epithelial antigen of the prostate 1 (STEAP1). J Biol Chem 295: 9502-9512, 2020.
37. Li YJ, Wang Y and Wang YY: MicroRNA-99b suppresses human cervical cancer cell activity by inhibiting the PI3K/AKT/mTOR signaling pathway. J Cell Physiol 234: 9577-9591, 2019.
38. Bhatia V, Kamat NV, Pariva TE, Wu LT, Tsao A, Sasaki K, Sun H, Javier G, Nutt S, Coleman I, *et al*: Targeting advanced prostate cancer with STEAP1 chimeric antigen receptor T cell and tumor-localized IL-12 immunotherapy. Nat Commun 14: 2041, 2023.
39. Thorne AH, Malo KN, Wong AJ, Nguyen TT, Cooch N, Reed C, Yan J, Broderick KE, Smith TRF, Masteller EL and Humeau L: Adjuvant screen identifies synthetic DNA-Encoding Flt3L and CD80 immunotherapeutics as candidates for enhancing anti-tumor T cell responses. Front Immunol 11: 327, 2020.
40. Sperger JM, Helzer KT, Stahlfeld CN, Jiang D, Singh A, Kaufmann KR, Niles DJ, Heninger E, Rydzewski NR, Wang L, *et al*: Expression and therapeutic targeting of TROP-2 in treatment-resistant prostate cancer. Clin Cancer Res 29: 2324-2335, 2023.
41. Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, Moroose R, Santin AD, Kalinsky K, Picozzi V, *et al*: Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: Final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Ann Oncol 32: 746-756, 2021.
42. Matera L: The choice of the antigen in the dendritic cell-based vaccine therapy for prostate cancer. Cancer Treat Rev 36: 131-41, 2010.
43. Chen L, Chen F, Niu H, Li J, Pu Y, Yang C, Wang Y, Huang R, Li K, Lei Y and Huang Y: Chimeric antigen receptor (CAR)-T cell immunotherapy against thoracic malignancies: Challenges and opportunities. Front Immunol 13: 871661, 2022.
44. Puca L, Gavyert K, Sailer V, Conteduca V, Dardenne E, Sigouros M, Isse K, Kearney M, Vosoughi A, Fernandez L, *et al*: Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med 11: eaav0891, 2019.
45. Mohsin H, Jia F, Sivaguru G, Hudson MJ, Shelton TD, Hoffman TJ, Cutler CS, Ketring AR, Athey PS, Simón J, *et al*: Radiolanthanide-labeled monoclonal antibody CC49 for radioimmunotherapy of cancer: Biological comparison of DOTA conjugates and 149Pm, 166Ho, and 177Lu. Bioconjug Chem 17: 485-492, 2006.
46. Van Emmenis L, Ku SY, Gayvert K, Branch JR, Brady NJ, Basu S, Russell M, Cyrta J, Vosoughi A, Sailer V, *et al*: The identification of CELSR3 and other potential cell surface targets in neuroendocrine prostate cancer. Cancer Res Commun 3: 1447-1459, 2023.
47. Hong S, Jeong SH, Han JH, Yuk HD, Jeong CW, Ku JH and Kwak C: Highly efficient nucleic acid encapsulation method for targeted gene therapy using antibody conjugation system. Mol Ther Nucleic Acids 35: 102322, 2024.
48. Patell K, Kurian M, Garcia JA, Mendiratta P, Barata PC, Jia AY, Spratt DE and Brown JR: Lutetium-177 PSMA for the treatment of metastatic castrate resistant prostate cancer: A systematic review. Expert Rev Anticancer Ther 23: 731-744, 2023.

49. Fallah J, Agrawal S, Gittleman H, Fiero MH, Subramaniam S, John C, Chen W, Ricks TK, Niu G, Fotenos A, *et al*: FDA approval summary: Lutetium Lu 177 Vipivotide tetraxetan for patients with metastatic castration-resistant prostate cancer. Clin Cancer Res 29: 1651-1657, 2023.
50. Tschan VJ, Busslinger SD, Bernhardt P, Grundler PV, Zeevaart JR, Köster U, van der Meulen NP, Schibli R and Müller C: Albumin-binding and conventional PSMA ligands in combination with 161Tb: Biodistribution, dosimetry, and preclinical therapy. J Nucl Med 64: 1625-1631, 2023.
51. Buteau JP, Kostos L, Jackson PA, Xie J, Haskali MB, Alipour R, McIntosh LE, Emmerson B, MacFarlane L, Martin CA, *et al*: First-in-human results of terbium-161 [161Tb] Tb-PSMA-I&T dual beta-Auger radioligand therapy in patients with metastatic castration-resistant prostate cancer (VIOLET): A single-centre, single-arm, phase 1/2 study. Lancet Oncol 26: 1009-1017, 2025.
52. Mark C, Lee JS, Cui X and Yuan Y: Antibody-drug conjugates in breast cancer: Current status and future directions. Int J Mol Sci 24: 13726, 2023.
53. Wang Y, Li G, Wang H, Qi Q, Wang X and Lu H: Targeted therapeutic strategies for Nectin-4 in breast cancer: Recent advances and future prospects. Breast 79: 103838, 2025.
54. Nguyen H, Hird K, Cardaci J, Smith S and Lenzo NP: Lutetium-177 Labelled Anti-PSMA monoclonal antibody (Lu-TLX591) Therapy for metastatic prostate cancer: Treatment toxicity and outcomes. Mol Diagn Ther 28: 291-299, 2024.
55. Yassin MT, Al-Otibi FO, Al-Sahli SA, El-Wetidy MS and Mohamed S: Metal oxide nanoparticles as efficient nanocarriers for targeted cancer therapy: Addressing chemotherapy-induced disabilities. Cancers (Basel) 16: 4234, 2024.
56. Huang C, Duan X, Wang J, Tian Q, Ren Y, Chen K, Zhang Z, Li Y, Feng Y, Zhong K, *et al*: Lipid nanoparticle delivery system for mRNA encoding B7H3-redirected bispecific antibody displays potent antitumor effects on malignant tumors. Adv Sci (Weinh) 10: e2205532, 2023.
57. Deegen P, Thomas O, Nolan-Stevaux O, Li S, Wahl J, Bogner P, Aeffner F, Friedrich M, Liao MZ, Matthes K, Rau D, *et al*: The PSMA-targeting half-life extended BiTE therapy AMG 160 has potent antitumor activity in preclinical models of metastatic castration-resistant prostate cancer. Clin Cancer Res 27: 2928-2937, 2021.
58. Wei M, Zuo S, Chen Z, Qian P, Zhang Y, Kong L, Gao H, Wei J and Dong J: Oncolytic vaccinia virus expressing a bispecific T-cell engager enhances immune responses in EpCAM positive solid tumors. Front Immunol 13: 1017574, 2022.
59. Ayzman A, Pachynski RK and Reimers MA: PSMA-based therapies and novel therapies in advanced prostate cancer: The now and the future. Curr Treat Options Oncol 26: 375-384, 2025.
60. Jin Y, Lorvik KB, Jin Y, Beck C, Sike A, Persiconi I, Kvaløy E, Saatcioglu F, Dunn C and Kyte JA: Development of STEAP1 targeting chimeric antigen receptor for adoptive cell therapy against cancer. Mol Ther Oncolytics 26: 189-206, 2022.
61. Si M, Xia Y, Cong M, Wang D, Hou Y and Ma H: In situ co-delivery of doxorubicin and cisplatin by Injectable thermosensitive hydrogels for enhanced osteosarcoma treatment. Int J Nanomedicine 17: 1309-1322, 2022.
62. Tu Z, Chen Y, Zhang Z, Meng W and Li L: Barriers and solutions for CAR-T therapy in solid tumors. Cancer Gene Ther 32: 923-934, 2025.
63. Kim YJ, Li W, Zhelev DV, Mellors JW, Dimitrov DS and Baek DS: Chimeric antigen receptor-T cells are effective against CEACAM5 expressing non-small cell lung cancer cells resistant to antibody-drug conjugates. Front Oncol 13: 1124039, 2023.
64. Jiang Y, Wen W, Yang F, Han D, Zhang W and Qin W: Prospect of prostate cancer treatment: Armed CAR-T or combination therapy. Cancers (Basel) 14: 967, 2022.
65. Wala JA and Hanna GJ: Chimeric antigen receptor T-cell therapy for solid tumors. Hematol Oncol Clin North Am 37: 1149-1168, 2023.
66. Bains RS, Raju TG, Semaan LC, Block A, Yamaguchi Y, Priceman SJ, George SC and Shirure VS: Vascularized tumor-on-a-chip to investigate immunosuppression of CAR-T cells. Lab Chip 25: 2390-2400, 2025.
67. Norde WJ, Hobo W, van der Voort R and Dolstra H: Coinhibitory molecules in hematologic malignancies: Targets for therapeutic intervention. Blood 120: 728-736, 2012.
68. Alavi SE, Ebrahimi Shahmabadi H, Sharma LA and Sharma A: Nanoparticle-based drug delivery systems for non-surgical periodontal therapy: Innovations and clinical applications. 3 Biotech 15: 269, 2025.
69. Guo F, Luo S, Wang L, Wang M, Wu F, Wang Y, Jiao Y, Du Y, Yang Q, Yang X and Yang G: Protein corona, influence on drug delivery system and its improvement strategy: A review. Int J Biol Macromol 256 (Pt 2): 128513, 2024.
70. Guo L, Shi D, Shang M, Sun X, Meng D, Liu X, Zhou X and Li J: Utilizing RNA nanotechnology to construct negatively charged and ultrasound-responsive nanodroplets for targeted delivery of siRNA. Drug Deliv 29: 316-327, 2022.
71. Seifert R, Kessel K, Schlack K, Weckesser M, Kersting D, Seitzer KE, Weber M, Bögemann M and Rahbar K: Total tumor volume reduction and low PSMA expression in patients receiving Lu-PSMA therapy. Theranostics 11: 8143-8151, 2021.
72. Shih CH, Hsieh TY and Sung WW: Prostate-specific membrane antigen-targeted antibody-drug conjugates: A promising approach for metastatic castration-resistant prostate cancer. Cells 14: 513, 2025.
73. Liu D, Bao L, Zhu H, Yue Y, Tian J, Gao X and Yin J: Microenvironment-responsive anti-PD-L1 x CD3 bispecific T-cell engager for solid tumor immunotherapy. J Control Release 354: 606-614, 2023.
74. Tan B, Tu C, Xiong H, Xu Y, Shi X, Zhang X, Yang R, Zhang N, Lin B, Liu M, *et al*: GITRL enhances cytotoxicity and persistence of CAR-T cells in cancer therapy. Mol Ther 33: 2789-2800, 2025.
75. Techaapornkun P, Rojpalakorn W, Mejun N, Khaniya A, Thammahong A, Thu MS, Hirankarn N and Pitakkitnukun P: Comparative efficacy and safety of BCMA-targeted CAR T cells and BiTEs in relapsed/refractory multiple myeloma: A meta-analysis of interventional and real-world studies. Ann Hematol 104: 4791-4809, 2025.
76. Bolsée J, Violle B, Jacques-Hespel C, Nguyen T, Lonez C and Breman E: Tandem CAR T-cells targeting CD19 and NKG2DL can overcome CD19 antigen escape in B-ALL. Front Immunol 16: 1557405, 2025.
77. Yamamichi G, Kato T, Watabe T, Hatano K, Uemura M and Nonomura N: Current status of prostate-specific membrane antigen-targeted alpha radioligand therapy in prostate cancer. Anticancer Res 44: 879-888, 2024.
78. Zhang Q, Helfand BT, Carneiro BA, Qin W, Yang XJ, Lee C, Zhang W, Giles FJ, Cristofanilli M and Kuzel TM: Efficacy against human prostate cancer by prostate-specific membrane antigen-specific, transforming growth Factor-β insensitive genetically targeted CD8+ T-cells derived from patients with metastatic castrate-resistant disease. Eur Urol 73: 648-652, 2018.
79. Guedan S and Delgado J: Immobilizing a moving target: CAR T cells hit CD22. Clin Cancer Res 25: 5188-5190, 2019.
80. Song EZ, Wang X, Philipson BI, Zhang Q, Thokala R, Zhang L, Assenmacher CA, Binder ZA, Ming GL, O'Rourke DM, *et al*: The IAP antagonist birinapant enhances chimeric antigen receptor T cell therapy for glioblastoma by overcoming antigen heterogeneity. Mol Ther Oncolytics 27: 288-304, 2022.
81. Peter J, Toppeta F, Trubert A, Danhof S, Hudecek M and Däullary T: Multi-Targeting CAR-T cell strategies to overcome immune evasion in lymphoid and myeloid malignancies. Oncol Res Treat 48: 265-279, 2025.
82. Borcoman E, Kamal M, Marret G, Dupain C, Castel-Ajgal Z, Le Tourneau C: HDAC inhibition to prime immune checkpoint inhibitors. Cancers (Basel) 14: 66, 2021.
83. López-Collazo E, Hurtado-Navarro L: Cell fusion as a driver of metastasis: Re-evaluating an old hypothesis in the age of cancer heterogeneity. Front Immunol 16: 1524781, 2025.
84. Derderian S, Vesval Q, Wissing MD, Hamel L, Côté N, Vanhuyse M, Ferrario C, Bladou F, Aprikian A and Chevalier S: Liquid biopsy-based targeted gene screening highlights tumor cell subtypes in patients with advanced prostate cancer. Clin Transl Sci 15: 2597-2612, 2022.
85. Tserunyan V and Finley SD: Modelling predicts differences in chimeric antigen receptor T-cell signalling due to biological variability. R Soc Open Sci 9: 220137, 2022.
86. Fan J, Zhu J, Zhu H and Xu H: Potential therapeutic targets in myeloid cell therapy for overcoming chemoresistance and immune suppression in gastrointestinal tumors. Crit Rev Oncol Hematol 198: 104362, 2024.
87. Wang H, Liu S, Zhan J, Liang Y and Zeng X: Shaping the immune-suppressive microenvironment on tumor-associated myeloid cells through tumor-derived exosomes. Int J Cancer 154: 2031-2042, 2024.
88. Kemp SB, Pasca di Magliano M and Crawford HC: Myeloid cell mediated immune suppression in pancreatic cancer. Cell Mol Gastroenterol Hepatol 12: 1531-1542, 2021.

89. Kerr MD, McBride DA, Chumber AK and Shah NJ: Combining therapeutic vaccines with chemo- and immunotherapies in the treatment of cancer. Expert Opin Drug Discov 16: 89-99, 2021.
90. Ganaie AA, Mansini AP, Hussain T, Rao A, Siddique HR, Shabaneh A, Ferrari MG, Murugan P, Klingelhöfer J, Wang J, *et al*: Anti-S100A4 antibody therapy is efficient in treating aggressive prostate cancer and reversing immunosuppression: Serum and biopsy S100A4 as a clinical predictor. Mol Cancer Ther 19: 2598-2611, 2020.
91. Wang K, Hao Z, Fu X, Li W, Jiao A and Hua X: Involvement of elevated ASF1B in the poor prognosis and tumorigenesis in pancreatic cancer. Mol Cell Biochem 477: 1947-1957, 2022.
92. Kim B, Jung S, Kim H, Kwon JO, Song MK, Kim MK, Kim HJ and Kim HH: The role of S100A4 for bone metastasis in prostate cancer cells. BMC Cancer 21: 137, 2021.
93. Peng S, Hu P, Xiao YT, Lu W, Guo D, Hu S, Xie J, Wang M, Yu W, Yang J, *et al*: Single-cell analysis reveals EP4 as a target for restoring T-cell infiltration and sensitizing prostate cancer to immunotherapy. Clin Cancer Res 28: 552-567, 2022.
94. Yan J, Wang Y, Jia Y, Liu S, Tian C, Pan W, Liu X and Wang H: Co-delivery of docetaxel and curcumin prodrug via dual-targeted nanoparticles with synergistic antitumor activity against prostate cancer. Biomed Pharmacother 88: 374-383, 2017.
95. Zhuang R, Xie R, Peng S, Zhou Q, Lin W, Ou Y, Chen B, Su T, Li Z, Huang H, *et al*: An anti-androgen resistance-related gene signature acts as a prognostic marker and increases enzalutamide efficacy via PLK1 inhibition in prostate cancer. J Transl Med 23: 480, 2025.
96. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, *et al*: Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 385: 1091-1103, 2021.
97. Vakil V and Trappe W: Drug-resistant cancer treatment strategies based on the dynamics of clonal evolution and PKPD modeling of drug combinations. IEEE/ACM Trans Comput Biol Bioinform 19: 1603-1614, 2022.
98. Xu J, Yang X, Deshmukh D, Chen H, Fang S and Qiu Y: The role of crosstalk between AR3 and E2F1 in drug resistance in prostate cancer cells. Cells 9: 1094, 2020.
99. Chatzilygeroudi T, Karantanos T and Pappa V: Unraveling venetoclax resistance: Navigating the future of HMA/Venetoclax-Refractory AML in the molecular era. Cancers (Basel) 17: 1586, 2025.
100. Saad F: Should only patients with BRCA mutation be treated with a combination of an androgen receptor pathway inhibitor and a PARP inhibitor for metastatic castration-resistant prostate cancer? The answer is no. Eur Urol Focus 10: 506-508, 2024.
101. Hachem S, Yehya A, El Masri J, Mavingire N, Johnson JR, Dwead AM, Kattour N, Bouchi Y, Kobeissy F, Rais-Bahrami S, *et al*: Contemporary update on clinical and experimental prostate cancer biomarkers: A multi-omics-focused approach to detection and risk stratification. Biology (Basel) 13: 762, 2024.
102. Chen Y, Fan X, Lu R, Zeng S and Gan P: PARP inhibitor and immune checkpoint inhibitor have synergism efficacy in gallbladder cancer. Genes Immun 25: 307-316, 2024.
103. Kumar M, Nguyen TPN, Kaur J, Singh TG, Soni D, Singh R and Kumar P: Opportunities and challenges in application of artificial intelligence in pharmacology. Pharmacol Rep 75: 3-18, 2023.
104. Danila DC, Szmulewitz RZ, Vaishampayan U, Higano CS, Baron AD, Gilbert HN, Brunstein F, Milojic-Blair M, Wang B, Kabbarah O, *et al*: Phase I study of DSTP3086S, an antibody-drug conjugate targeting six-transmembrane epithelial antigen of prostate 1, in metastatic castration-resistant prostate cancer. J Clin Oncol 37: 3518-3527, 2019.
105. Paoletti C and Hayes DF: Circulating tumor cells. Adv Exp Med Biol 882: 235-258, 2016.
106. Vis DJ, Palit SAL, Corradi M, Cuppen E, Mehra N, Lolkema MP, Wessels LFA, van der Heijden MS, Zwart W and Bergman AM: Whole genome sequencing of 378 prostate cancer metastases reveals tissue selectivity for mismatch deficiency with potential therapeutic implications. Genome Med 17: 24, 2025.
107. van der Sar ECA, Kühr AJS, Ebbers SC, Henderson AM, de Keizer B, Lam MGEH and Braat AJAT: Baseline imaging derived predictive factors of response following [177Lu] Lu-PSMA-617 therapy in salvage metastatic castration-resistant prostate cancer: A lesion- and patient-based analysis. Biomedicines 10: 1575, 2022.
108. Hwang C, Henderson NC, Chu SC, Holland B, Cackowski FC, Pilling A, Jang A, Rothstein S, Labriola M, Park JJ, *et al*: Biomarker-directed therapy in black and white men with metastatic castration-resistant prostate cancer. JAMA Netw Open 6: e2334208, 2023.
109. Parghane RV and Basu S: PSMA-targeted radioligand therapy in prostate cancer: Current status and future prospects. Expert Rev Anticancer Ther 23: 959-975, 2023.
110. Petrylak DP, Vogelzang NJ, Chatta K, Fleming MT, Smith DC, Appleman LJ, Hussain A, Modiano M, Singh P, Tagawa ST, *et al*: PSMA ADC monotherapy in patients with progressive metastatic castration-resistant prostate cancer following abiraterone and/or enzalutamide: Efficacy and safety in open-label single-arm phase 2 study. Prostate 80: 99-108, 2020.
111. Thang SP, Violet J, Sandhu S, Iravani A, Akhurst T, Kong G, Ravi Kumar A, Murphy DG, Williams SG, Hicks RJ and Hofman MS: Poor outcomes for patients with metastatic castration-resistant prostate cancer with low prostate-specific membrane antigen (PSMA) expression deemed ineligible for 177Lu-labelled PSMA radioligand therapy. Eur Urol Oncol 2: 670-676, 2019.
112. Fu Y, Urban DJ, Nani RR, Zhang YF, Li N, Fu H, Shah H, Gorka AP, Guha R, Chen L, *et al*: Glypican-3-specific antibody drug conjugates targeting hepatocellular carcinoma. Hepatology 70: 563-576, 2019.
113. Xu J, Liu W, Fan F, Zhang B, Sun C and Hu Y: Advances in nano-immunotherapy for hematological malignancies. Exp Hematol Oncol 13: 57, 2024.
114. Cao P and Bae Y: Polymer nanoparticulate drug delivery and combination cancer therapy. Future Oncol 8: 1471-1480, 2012.
115. Paschalis A, Sheehan B, Riisnaes R, Rodrigues DN, Gurel B, Bertan C, Ferreira A, Lambros MBK, Seed G, Yuan W, *et al*: Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. Eur Urol 76: 469-478, 2019.
116. Hong J, Bae S, Cavinato L, Seifert R, Ryhiner M, Rominger A, Erlandsson K, Wilks M, Normandin M, El-Fakhri G, *et al*: Deciphering the effects of radiopharmaceutical therapy in the tumor microenvironment of prostate cancer: An in-silico exploration with spatial transcriptomics. Theranostics 14: 7122-7139, 2024.
117. Narayana RVL and Gupta R: Exploring the therapeutic use and outcome of antibody-drug conjugates in ovarian cancer treatment. Oncogene 44: 2343-2356, 2025.
118. Grosso C, Silva A, Delerue-Matos C and Barroso MF: Single and multitarget systems for drug delivery and detection: Up-to-date strategies for brain disorders. Pharmaceuticals (Basel) 16: 1721, 2023.
119. Yeh CY, Hsiao JK, Wang YP, Lan CH and Wu HC: Peptide-conjugated nanoparticles for targeted imaging and therapy of prostate cancer. Biomaterials 99: 1-15, 2016.
120. Bimbatti D, Maruzzo M, Pierantoni F, Diminutto A, Dionese M, Deppieri FM, Lai E, Zagonel V and Basso U: Immune checkpoint inhibitors rechallenge in urological tumors: An extensive review of the literature. Crit Rev Oncol Hematol 170:103579, 2022.
121. McMullan C, Turner G, Retzer A, Belli A, Davies EH, Nice L, Flavell L, Flavell J and Calvert M: Testing an electronic patient-reported outcome platform in the context of traumatic brain injury: PRiORiTy usability study. JMIR Form Res 9: e58128, 2025.
122. Ramos-Casals M and Sisó-Almirall A: Immune-related adverse events of immune checkpoint inhibitors. Ann Intern Med 177: ITC17-ITC32, 2024.
123. Naing A, Hajjar J, Gulley JL, Atkins MB, Ciliberto G, Meric-Bernstam F and Hwu P: Strategies for improving the management of immune-related adverse events. J Immunother Cancer 8: e001754, 2020.
124. Ong SY and Baird JH: A primer on chimeric antigen receptor T-cell therapy-related toxicities for the intensivist. J Intensive Care Med 39: 929-938, 2024.
125. Ciano-Petersen NL, Muñiz-Castrillo S, Vogrig A, Joubert B and Honnorat J: Immunomodulation in the acute phase of autoimmune encephalitis. Rev Neurol (Paris) 178: 34-47, 2022.