

Nanomedicine Targeting Cancer-Associated Fibroblasts in Prostate Cancer: From Biological Mechanisms to Integrated Theranostic Strategies

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Abstract: Prostate cancer (PCa) is the second most common malignancy in men worldwide. Advanced stages are characterized by tumor heterogeneity, metastasis, and resistance to androgen deprivation therapy and chemotherapy. Cancer-associated fibroblasts (CAFs), the predominant stromal cells in the PCa tumor microenvironment (TME), critically drive tumor progression, metastasis, and therapeutic resistance. Nanomedicine represents a transformative strategy for targeting CAFs. It leverages engineered nanomaterials to achieve precise drug delivery, improved bioavailability, and multimodal theranostic capabilities, which integrate diagnosis with therapy. This review comprehensively examines advances in nanomaterial-based strategies for CAF-targeted therapy in PCa. We first delineate the biology of CAFs in PCa, encompassing their origins, activation mechanisms, key markers (e.g., α -SMA and FAP), phenotypic heterogeneity, and intricate crosstalk with cancer cells, immune cells, and the extracellular matrix (ECM). We then evaluate nanomaterial-based targeting strategies and therapeutic modalities, including CAF depletion, reprogramming, and extracellular matrix remodeling, for the treatment of PCa. Subsequently, we discuss CAF-targeted nanoplateforms for theranostics, including molecular imaging probes (e.g., ⁶⁸Ga-FAPI) and image-guided delivery systems that integrate precise diagnosis with therapy. Finally, we address key challenges, particularly CAF heterogeneity and nanomaterial biosafety, and outline future directions, including gene-editing integration, multi-stimuli-responsive systems, and synergistic immunotherapy combinations. Collectively, this review underscores the transformative potential of integrating CAF biology with nanotechnology to overcome therapeutic resistance in PCa and advance precision oncology.

Keywords: cancer-associated fibroblasts, prostate cancer, tumor microenvironment, nanomedicine, diagnostics and therapeutics, targeted therapy

Introduction

Prostate cancer (PCa) is the second most common malignancy in men worldwide, accounting for approximately 7.8% of all cancer cases.¹ It is particularly prevalent in individuals over 65 and exhibits higher incidence rates in regions such as Africa and Northern Europe.² Standard treatments, including surgery, androgen deprivation therapy (ADT), radiotherapy, and chemotherapy, have substantially improved the prognosis of localized disease. However, the management of advanced and metastatic PCa remains challenging, largely due to tumor heterogeneity, metastatic dissemination, and acquired therapeutic resistance.³ For example, while radical prostatectomy can be curative for organ-confined tumors,

microscopic residual disease may persist and contribute to biochemical recurrence and subsequent metastasis. Similarly, ADT targets the androgen receptor (AR) pathway, a central driver of PCa progression. However, tumors frequently evolve into castration-resistant PCa (CRPC) through mechanisms including AR amplification, ligand-independent activation, and crosstalk with immune components like tumor-associated macrophages (TAMs). TAMs secrete cytokines such as IL-6 and IGF-1 to sustain AR signaling under castration conditions.⁴ Increasing evidence suggests that these resistance mechanisms are not solely cancer cell-intrinsic but are profoundly influenced by the tumor microenvironment (TME). The TME is a dynamic and complex ecosystem composed of malignant epithelial cells, immune cells, endothelial cells, and stromal populations, including cancer-associated fibroblasts (CAFs).^{5,6} Accumulating studies indicate that CAFs play a critical role in the pathogenesis and progression of PCa.⁷ As the most abundant stromal cells in the TME, CAFs play a pivotal role in tumor progression by remodeling the extracellular matrix (ECM), secreting growth factors (e.g., Transforming Growth Factor Beta (TGF- β), HGF, C-X-C Motif Chemokine Ligand 12 (CXCL12)), promoting angiogenesis, and facilitating immune evasion.⁸ In PCa, CAFs exhibit heterogeneity in both their cellular origins and marker expression. They can originate from resident fibroblasts, mesenchymal stem cells, and perivascular cells, and express markers such as α -SMA, FAP, and PDGFR β .⁹ It is increasingly recognized that distinct CAF subpopulations exert context-dependent functions within the TME. Through reciprocal crosstalk with PCa cells, CAFs can facilitate epithelial-mesenchymal transition (EMT), metabolic reprogramming, immune evasion, and therapy resistance.¹⁰ Although many of these findings are derived from preclinical models and correlative clinical observations, they collectively support a functional role for CAFs in adverse clinical outcomes. CAF heterogeneity further contributes to the dynamic evolution of prostate tumors. CAF-mediated signaling pathways, including Wnt/ β -catenin and TGF- β signaling, have been implicated in tumor progression and resistance phenotypes.⁶ Due to their abundance, plasticity, and multifaceted functions, CAFs have emerged as promising—yet complex—therapeutic and diagnostic targets in PCa. Therefore, the biological complexity of CAFs presents them as potential therapeutic and diagnostic targets in PCa. Advances in nanomedicine offer promising opportunities to target the interactions between CAFs and PCa cells. Nanoparticles (NPs) can improve drug solubility, extend circulation half-life, enable targeted delivery via passive (e.g., the enhanced permeability and retention (EPR) effect) or active targeting, and facilitate multimodal theranostic approaches that combine imaging with chemo-immunotherapy.^{11,12} Despite these advancements, current therapeutic paradigms predominantly target cancer cells and often neglect the supportive role of CAFs in sustaining tumor growth and therapy resistance. For instance, while prostate-specific membrane antigen (PSMA)-targeted NPs can enhance radiotherapy sensitivity and reduce off-target effects, systematic strategies to modulate CAFs remain underexplored.¹³ However, systematic approaches specifically designed to modulate CAF biology in PCa remain relatively underexplored. Key limitations include limited tumor penetration due to dense ECM deposition, potential systemic toxicity associated with nonspecific biodistribution, and an incomplete understanding of CAF subtypes—such as myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs)—and their dynamic functional states within the TME.¹⁴ Moreover, although nanomaterial-based strategies have shown encouraging results in targeting CAFs in other solid tumors, including pancreatic and breast cancers (for example, partial reduction of ECM deposition and stromal normalization in preclinical models), direct evidence supporting analogous efficacy in PCa remains comparatively limited. A comprehensive review that integrates CAF biology, nanomaterial design principles, and PCa-specific therapeutic strategies is therefore needed. Addressing this knowledge gap may facilitate the rational development and clinical translation of CAF-targeted nanomedicines, particularly in the context of CRPC and metastatic disease.

This review addresses these challenges by synthesizing current knowledge of CAF biology in PCa, identifying key CAF-associated molecular targets and signaling pathways, and evaluating nanomedicine platforms designed for CAF-focused interventions. We propose that integrating CAF-specific targeting strategies with multifunctional nanoparticles, such as selective CAF depletion, phenotypic reprogramming, extracellular matrix modulation, and combination immunotherapy—may enhance therapeutic efficacy and help mitigate drug resistance. By examining key nanoparticle design parameters, including size, surface charge, and surface functionalization, as well as stimulus-responsive features such as pH- or enzyme-sensitive systems, this review highlights opportunities for precision nanomedicine in PCa and its broader relevance to oncology, biomaterials science, and tumor immunology. The review is organized to discuss CAF biology,

nanomaterial classifications and applications, targeting strategies, therapeutic modalities, integrated theranostic platforms, current limitations, and future perspectives in a logical sequence.

The Biological Basis of CAFs in PCa

Origins and Activation of CAFs in PCa

CAFs constitute the most abundant stromal cell population within the PCa TME. They play crucial roles in tumor progression, metastasis, and therapy resistance, and exhibit significant functional heterogeneity stemming from their diverse cellular origins. CAFs in PCa are primarily derived from several sources, including tissue-resident fibroblasts (TRFs), mesenchymal stem cells (MSCs), and other cell types.^{14–16} Resident fibroblasts are activated by soluble paracrine factors, including TGF- β , osteopontin (OPN), a low extracellular pH, and progranulin (PGRN), which induce their phenotypic transformation into CAFs. PCa cells secrete diffusible factors (e.g., those related to TMPRSS2 and ITGA6), which establish a concentration gradient in the local microenvironment that drives the transformation of resident fibroblasts into CAFs.^{17,18} Pericytes can differentiate into myCAF subtypes. This process involves detachment from the vasculature, is stimulated by TGF- β , and is associated with the expression of markers such as PDGFR β and α -SMA. myCAFs contribute to aberrant tumor angiogenesis.^{10,19,20} Other important sources include adipose-derived stem cells (ASCs) from periprostatic fat and bone marrow-derived mesenchymal stem cells (BM-MSCs). Periprostatic adipose tissue (PPAT) secretes bioactive molecules that influence PCa cell growth, migration, and invasion.²¹ ASCs within the PPAT can differentiate into CAFs via paracrine signaling networks. These CAFs promote tumor progression through multifaceted effects, including inhibiting apoptosis, stimulating proliferation (mitogenesis), inducing angiogenesis, and suppressing immune responses. Furthermore, ASC-derived CAFs have been shown to enhance cancer cell invasion and chemoresistance. For example, work by Su et al demonstrated their role in modulating cancer cell oxidative stress signaling.^{10,16,22} BM-MSCs (BM-MSCs) are recruited to the tumor site via chemotactic signals such as TGF- β and the CXCL16/CXCR6 axis. Once integrated into the TME, BM-MSCs can promote PCa cell growth and invasion, as demonstrated in both in vitro and in vivo studies.^{10,23} Potential sources requiring further validation include: prostate epithelial cells, which may undergo malignant transformation induced by CAF paracrine signals;²⁴ and endothelial cells, which might undergo endothelial-to-mesenchymal transition (EndMT) in response to TGF- β , acquiring a fibroblast-like morphology and expressing markers such as fibroblast-specific protein-1 (FSP-1).¹⁰ Direct evidence for these origins in PCa remains limited. Collectively, these diverse cellular origins underpin the pronounced heterogeneity observed among CAF subtypes in PCa.

Phenotypic Markers and Detection Methods for CAFs in PCa

The in-depth analysis of specific markers has been instrumental in revealing the heterogeneity of CAFs and elucidating their functional roles in PCa. Because CAFs exhibit phenotypes distinct from normal fibroblasts (NFs), identifying and characterizing their markers is crucial. This effort not only clarifies CAF functions in tumor progression but also provides a foundation for clinical diagnosis, prognosis, and targeted therapy.²⁵ Alpha-smooth muscle actin (α -SMA) is a canonical CAF marker. It is a structural protein characteristic of smooth muscle cells and is highly expressed in activated CAFs. Its high expression correlates with a myofibroblast-like phenotype and is associated with stromal remodeling, tumor cell migration, and angiogenesis. α -SMA is commonly detected using immunohistochemistry (IHC) or flow cytometry.⁹ Fibroblast activation protein (FAP), a type II transmembrane serine protease, is another classic CAF marker involved in ECM remodeling. In PCa, FAP expression is significantly upregulated in tumor tissues and is often further elevated in metastatic lesions. Elevated FAP expression correlates with increased tumor aggressiveness and poor prognosis, making it a potential therapeutic target. FAP can be detected via IHC. Its expression profile is also discernible at the transcriptional level through single-cell RNA sequencing (scRNA-seq). CXCL12 is a key chemokine secreted by CAFs within the TME. It promotes tumor cell migration and invasion primarily by binding to its cognate receptor, C-X-C Motif Chemokine Receptor 4 (CXCR4). CXCL12 expression serves as a functional marker for CAFs in PCa, with its levels closely correlating with the metastatic potential of tumors. Its expression can be assessed at the mRNA level by quantitative reverse transcription polymerase chain reaction (qRT-PCR), at the protein level by enzyme-linked

immunosorbent assay (ELISA) or IHC.¹⁰ ScRNA-seq provides high-resolution transcriptomic profiling of CAFs within the TME. This technology has been pivotal in uncovering CAF heterogeneity and their complex interactions with tumor and immune cells. As the technology matures, scRNA-seq has become an indispensable tool for delineating CAF functions and subtypes.²⁶ Collectively, research into CAF markers provides a critical evidence base for improving PCa diagnosis, prognosis, and targeted therapy. A deeper understanding of CAF phenotype and function can enhance the clinical ability to predict tumor behavior, including growth, metastasis, and therapeutic response. Future CAF-targeted therapies, particularly those integrated with nanotechnology, hold promise for achieving more efficient drug delivery and improved therapeutic outcomes. Key CAF markers and their primary detection methods are summarized in Table 1.

CAF Heterogeneity: Subtype Classification and Functional Diversification

CAFs in PCa constitute a highly heterogeneous cell population. Based on distinct functional profiles within the TME, CAFs are categorized into several subtypes. These include myCAFs, iCAFs, apCAFs, matrix-remodeling CAFs

Table 1 Markers and Detection Methods of CAFs

Type	Indicator	Structural Essence	Detection Method	References
Transmembrane protease	FAP	Type II transmembrane serine protease	IHC, flow cytometry, scRNA-seq, mRNA sequencing	[9]
Transmembrane receptor	PDGFR α/β	Platelet-derived growth factor receptor	IHC, flow cytometry, scRNA-seq	[14]
ECM glycoprotein	Fibronectin I(FN1)	Fibronectin	IHC, scRNA-seq	[9]
	SPARC	Secreted protein, acidic and rich in cysteine	scRNA-seq, mRNA sequencing	[27]
	THBS2	Platelet-derived growth factor receptor 2	mRNA sequencing	[27]
Cytoskeletal protein	α -SMA	α -smooth muscle actin	IHC	[9]
	Vimentin (VIM)	Type III intermediate filament protein	Immunofluorescence, scRNA-seq	[14]
Membrane protein	CAV1	CAV1 caveolin I	IHC	[9]
ECM structural protein	COL1A1/COL1A2	Type I collagen	scRNA-seq, IHC, mRNA sequencing, functional secretion experiment	[27,28]
	COL3A1	Type III collagen	scRNA-seq, mRNA sequencing	[27]
ECM proteoglycan	DCN	Core proteoglycan	scRNA-seq (	[29]
	BGN	Biglycan	scRNA-seq (	[29]
	VCAN	versican	mRNA sequencing	[27]
ECM protein	POSTN	periostin	mRNA sequencing	[27]
ECM processing enzyme	ADAMTS2	procollagen N-endopeptidase	mRNA sequencing	[27]
Chromosome-associated protein	CENPF	centromere protein F	mRNA sequencing, IHC, functional experiments	[29]
Transmembrane	CD45 (PTPRC)	Type I transmembrane protein tyrosine phosphatase	Flow cytometry	[28]
Transcription factor	STAT2	Signal transducer and activator of transcription 2	scRNA-seq, immunofluorescence	[9]
Secreted growth factor	TGF- β	multifunctional secreted cytokine	QRT-PCR (ELISA, IHC (such as pSMAD2/3)	[10,30]
Secreted cytokine	IL-6	a pleiotropic pro-inflammatory cytokine	QRT-PCR, ELISA, and IHC	[14,30]
	CXCL12 (SDF-1)	CXC family chemokine	QRT-PCR, ELISA, IHC	[10]

(matCAFs), and CAFs associated with CRPC.³¹ Each subtype is defined by a unique gene expression signature and biological function, collectively contributing to key tumor processes such as progression, immune evasion, therapy resistance, and metastasis (Figure 1).²⁹

The myCAF subtype comprises highly activated fibroblasts characterized by abundant secretion of ECM components, including collagen I/III and fibronectin, which collectively increase stromal rigidity (Figure 2). myCAFs promote tumor angiogenesis (e.g., via Vascular Endothelial Growth Factor(VEGF)-A secretion) to enhance nutrient delivery and provide

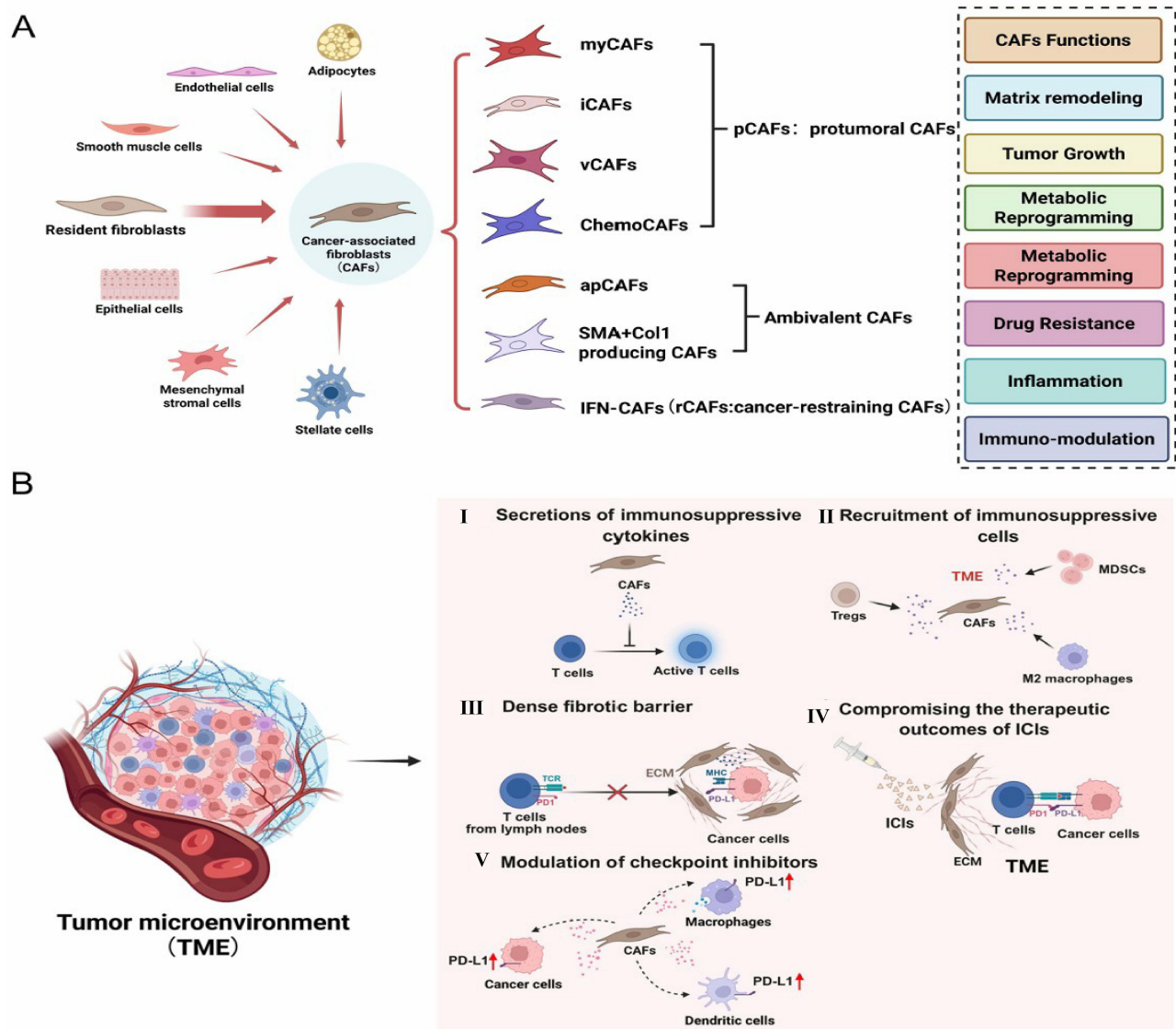


Figure 1 Origins, heterogeneity, and immunosuppressive roles of CAFs in the tumor microenvironment. **(A)** Putative cellular origins of cancer-associated fibroblasts (CAFs) and representative CAF subtypes. Solid arrows indicate proposed lineage contributions or transdifferentiation routes from resident fibroblasts and other precursor populations to CAFs. CAF subtypes are grouped as protumoral CAFs (pCAFs) and cancer-restraining CAFs (rCAFs/IFN-CAFs) as shown. The colored boxes summarize major CAF functions (e.g., matrix remodeling, tumor growth promotion, metabolic reprogramming, drug resistance, inflammation, and immunomodulation). **(B)** Schematic of CAF-driven immunosuppressive mechanisms within the tumor microenvironment (TME). Roman numerals denote distinct processes: I, secretion of immunosuppressive cytokines that impair T-cell activation; II, recruitment of immunosuppressive cells (e.g., Tregs, MDSCs, M2 macrophages) into the TME; III, formation of a dense fibrotic extracellular matrix (ECM) barrier that limits immune-cell infiltration; IV, attenuation of immune-checkpoint inhibitor (ICI) efficacy in the ECM-rich TME; V, modulation of immune-checkpoint pathways through myeloid and antigen-presenting cells. In **(B)**, dotted lines/particle clouds represent soluble mediators (cytokines/chemokines) released by CAFs or immune cells, and curved dashed arrows denote indirect regulatory effects within the TME. Upward arrows (↑) indicate increased expression (e.g., PD-L1↑). The red cross (×) indicates functional blockade or failure of effective T-cell access/engagement (e.g., exclusion by ECM barrier or impaired interaction with cancer cells). Reproduced from,³² Copyright © 2025 by authors.

Abbreviations: CAF, cancer-associated fibroblast; ECM, extracellular matrix; TME, tumor microenvironment; ICI, immune-checkpoint inhibitor; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; PD-1/PD-L1, programmed cell death protein 1/ligand 1; MHC, major histocompatibility complex.

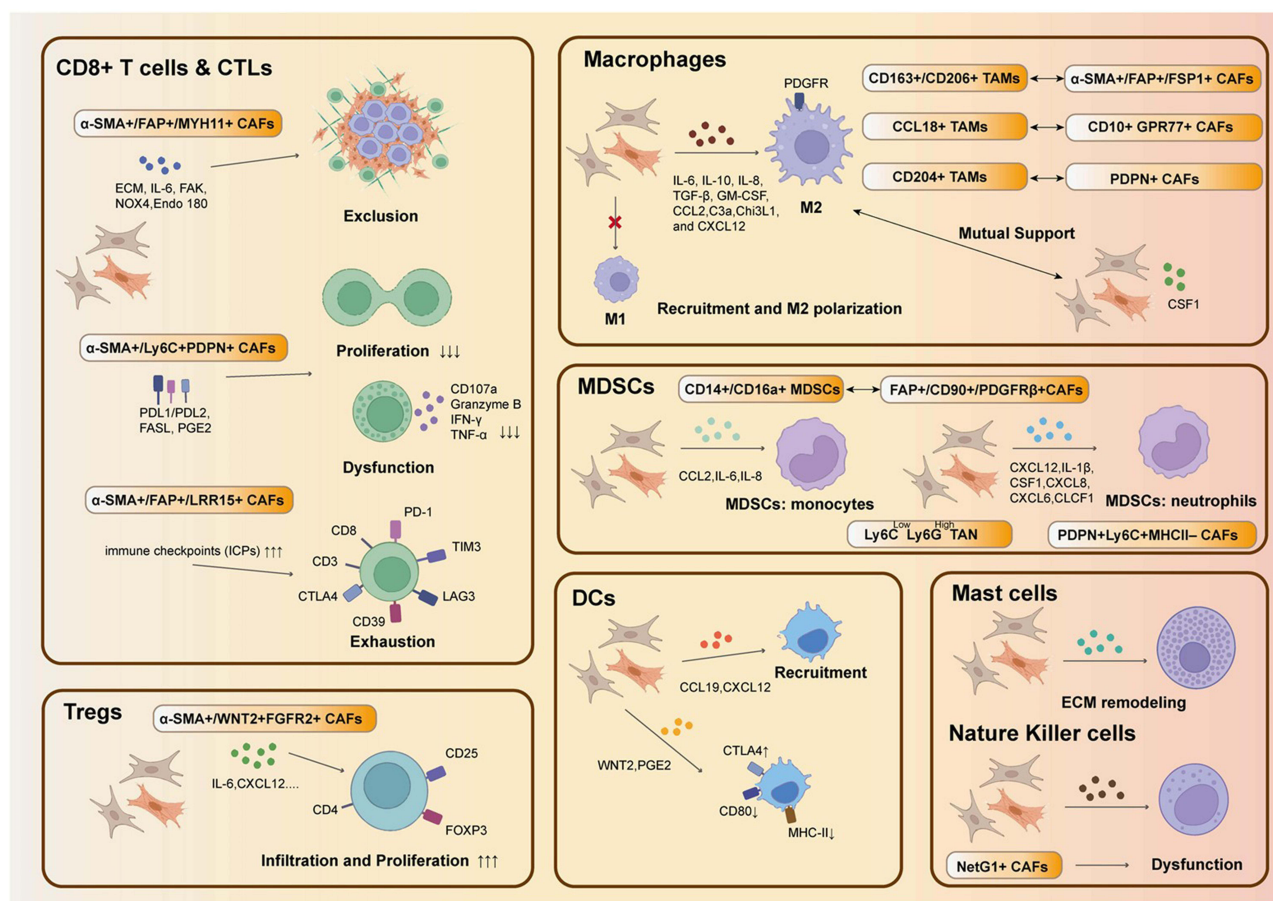


Figure 2 Crosstalk between cancer-associated fibroblasts (CAFs) and immune cells within the tumor microenvironment. This schematic summarizes CAF–immune interactions that collectively promote an immunosuppressive milieu. CD8⁺ T cells and cytotoxic T lymphocytes (CTLs) are inhibited by CAF-associated mechanisms leading to exclusion, reduced proliferation, dysfunction, and exhaustion. Regulatory T cells (Tregs) are promoted through CAF-derived factors that enhance infiltration and proliferation. Macrophages are recruited and polarized toward an M2-like phenotype by CAF-secreted cytokines and chemokines, while M2 tumor-associated macrophages (TAMs) provide reciprocal signals that support CAF activation, illustrating bidirectional reinforcement. Myeloid-derived suppressor cells (MDSCs) are recruited and maintained through CAF-derived mediators, with reciprocal pro-tumor interactions between CAFs and MDSC subsets. Dendritic cells (DCs) are affected by CAF-derived signals that alter recruitment and antigen-presenting function, and natural killer (NK) cells exhibit impaired effector function in the presence of CAF-associated cues. Mast cells are recruited and contribute to extracellular matrix (ECM) remodeling. Symbols and graphical elements: Solid arrows indicate directionality of signaling or functional influence between CAFs and immune cells. The red cross (×) denotes inhibition or blockade of a process (e.g., suppression of M1 polarization or impaired immune activation). Upward arrows (↑) and downward arrows (↓) indicate relative increases or decreases in the annotated markers or functions, respectively (e.g., increased immune checkpoint signaling; reduced effector molecule output). Multiple arrows (e.g., ↑↑↑ or ↓↓↓) indicate a stronger qualitative change. Where shown, bidirectional arrows represent reciprocal interactions or mutual support between cell types.

Abbreviations: CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; ECM, extracellular matrix; DC, dendritic cell; NK, natural killer cell; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; PD-1/PD-L1, programmed cell death protein 1/ligand 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; LAG3, lymphocyte-activation gene 3; TIM3, T-cell immunoglobulin and mucin domain 3. Reproduced from,³⁷ Copyright © 2024 by authors.

mechanical support for tumor growth.¹⁴ Phenotypic markers for myCAFs include α-SMA, PDGFRβ, TAGLN, and THY1 (CD90). Among these, THY1 (CD90) is considered a defining marker for myCAFs in the context of PCa, validated by proteomic and flow cytometric analyses of patient-matched CAF and normal fibroblasts.^{33,34} THY1 expression is enriched in high-risk patient cohorts and in CRPC, correlating directly with malignant disease progression.^{14,35} The iCAF subtype primarily promotes an immunosuppressive TME. iCAFs secrete a suite of pro-inflammatory cytokines and chemokines (e.g., IL-6, CXCL12, LIF, CCL2) that facilitate the infiltration of immunosuppressive cells like myeloid-derived suppressor cells (MDSCs) and inhibit cytotoxic CD8⁺ T cell function. Furthermore, iCAFs contribute to tumor immune escape. Preclinical evidence indicates that iCAFs are capable of transdifferentiating into a myCAF-like state following ADT, a process associated with increased tumor aggressiveness and therapy resistance in correlative clinical analyses. This therapy-induced phenotypic plasticity is not restricted to CAFs. In prostate cancer cells, ADT and AR signaling inhibitors have been shown to drive lineage reprogramming toward neuroendocrine prostate cancer (NEPC)

through epigenetic and transcriptional mechanisms.³⁶ This transition is associated with increased tumor aggressiveness and therapy resistance. iCAFs are phenotypically characterized by high expression of markers like PDGFR α and IL-6, both of which are key mediators of immunosuppression and therapy resistance in PCa. The apCAF subtype can present antigens and is implicated in modulating tumor immune evasion. Although apCAFs can engage T cells via antigen presentation, they typically lack essential costimulatory molecules. This often results in T cell anergy or exhaustion rather than productive activation.¹⁴ The key features of these CAF subtypes are summarized in Table 2. Notably, markers such as THY1 (CD90), PDGFR β , and CTHRC1 are expressed across multiple CAF subtypes, reflecting the heterogeneity and phenotypic plasticity of the CAF population.

CAF subtypes engage in dynamic and complex interactions. Therefore, a deeper understanding of subtype-specific markers and functions will provide a critical foundation for advancing precision medicine in PCa, enabling more accurate diagnosis, prognosis, and the development of novel therapies such as those employing nanomaterials.

Interactions Between CAFs and Other TME Components

Within the PCa TME, CAFs constitute the predominant stromal cell population. They function not as passive structural scaffolds but as active collaborators, critically driving tumor progression, therapy resistance, and immune evasion. These outcomes are mediated through intricate, multidimensional crosstalk between CAFs and various TME components, including cancer cells, immune cells, the vascular and nervous systems, and distant sites like the bone marrow.⁷ Interactions with cancer cells are multifaceted. CAFs engage in a symbiotic relationship, primarily through two major axes. First, a TGF- β /EMT positive feedback loop is established: CAF-derived TGF- β 1 induces EMT in cancer cells, which in turn further activates CAFs and amplifies TGF- β 1 secretion.⁴⁷ Second, CAFs promote metabolic reprogramming by delivering the long non-coding RNA MALAT1 to cancer cells via exosomes. This shifts cancer cell metabolism towards glycolysis, increasing lactate production and enhancing proliferation, invasion, and chemoresistance.^{48,49} In advanced PCa, CAFs also influence the DLL3-Notch signaling pathway to promote neuroendocrine differentiation and

Table 2 Subtypes of CAFs in PCa

CAFs Subtypes	Representative Marker Genes	Main Functions	References
myCAF	α -SMA (ACTA2), PDGFR β , TAGLN, CTHRC1, THY1, FNI, ITGA8, MACFI	Promotes ECM deposition and contraction, cell–matrix adhesion, and cytoskeletal organization; enhances angiogenesis and stromal stiffness; enriched in high-risk PCa and CRPC.	[14,35,38,39]
iCAF	IL-6, CXCL12, LIF, CCL2, CXCL14, PDGFR α	Secreting pro-inflammatory cytokines/chemokines (IL-6, CXCL12, PDGFR α ; signature conserved from PDAC); recruits MDSCs and inhibits CD8 ⁺ T cells (validated in murine PCa co-culture); capable of transdifferentiating into a myCAF-like phenotype following ADT (preclinical models, human PCa organoids); enriched in post-ADT patient biopsies (bulk RNA-seq, IHC).	[14,34,36,40]
apCAF	MHC-II (HLA-DR), CD74, CTSK, MRC2	Identified in PCa by scRNA-seq and spatial transcriptomics; enriched in stroma adjacent to malignant glands versus adjacent normal tissue. Expresses MHC-II but lacks co-stimulatory molecules; may modulate CD4 ⁺ T cell responses, though its immunological role in PCa remains to be elucidated. High apCAF density is independently associated with increased risk of biochemical recurrence after radical prostatectomy (multivariable Cox: HR ~1.8, $p < 0.05$, adjusted for CAPRA-S) in two large cohorts. CTSK ⁺ MRC2 ⁺ subset previously linked to biochemical recurrence	[9,34,41]
matCAF	POSTN, COL10A1, CTHRC1, POSTN, COL1A1, DCN, FAP	Organizes ECM via collagen cross-linking and matrix stiffening; enriched in advanced tumors and associated with poor prognosis. Single-cell RNA-seq of HNSCC identifies matCAF as a matrix-producing CAF subset characterized by high expression of ECM-related genes (COL1A1, DCN, FAP) and enrichment in extracellular matrix organization pathways	[42–44]
CRPC-CAF	SPPI (Osteopontin), CD90 (THY1), CD29 (ITGB1), PDPN	Promotes EMT and drug resistance via paracrine SPPI. SPPI activates PI3K/AKT and ERK1/2 signaling, upregulates AR expression, induces EMT (E-cadherin decreases, N-cadherin increases, vimentin increases), and enhances tumor cell adhesion, migration, and enzalutamide resistance. Clinically, SPPI is elevated in CRPC and bone metastases, correlates with high Gleason score, lymph node metastasis, and poor disease-free survival, and is upregulated in enzalutamide-resistant models. CD90 ⁺ and PDPN ⁺ subsets enhance tumor cell invasion and stromal remodeling via TGF- β /MMP2/9	[45,46]

immune evasion. This involves internal and external mechanisms. Internally, DLL3 trans-represses the tumor-suppressive Notch pathway, as demonstrated by Ku et al.⁵⁰ Externally, CAF-secreted IL-6 activates STAT3,¹⁴ which can suppress the expression of Notch target genes like HES1, thereby inhibiting the pathway's output.⁵¹ Within the immune microenvironment, CAFs suppress anti-tumor immunity through chemical and physical strategies. Chemically, they secrete factors like TGF- β , CCL2, and CXCL12 to recruit and expand immunosuppressive cells, including Tregs and monocytic myeloid-derived suppressor cells (M-MDSCs), which in turn inhibit CD8⁺ cytotoxic T cell function.⁵² For example, in murine PCa models, CAFs demonstrate functional adaptability by secreting CCL2, IL-6, and CXCL12. This secretion drives the STAT3-dependent differentiation of monocytes into M-MDSCs, a pathway supported by related cytokine expression in human CAF transcriptomes. These cells then suppress antitumor immunity by impairing antigen presentation, generating ROS, and inhibiting T cell activation, thereby directly linking CAF activity to the clinically relevant immunosuppressive microenvironment.⁵³ Physically, CAFs deposit dense ECM components, primarily collagen, creating a barrier that physically excludes CD8⁺ T cells from infiltrating the tumor core.^{52,54} CAFs also influence distant microenvironments crucial for tumor progression and metastasis, including the vasculature, nervous system, and bone. Their effects can be summarized in three major aspects. They promote angiogenesis by releasing factors such as VEGF, thereby stimulating neovascularization that supports tumor growth.¹⁴ They also mediate neurotrophic signaling through molecules such as NGF, which can activate Trk receptors on cancer cells and promote perineural invasion and cancer-associated pain.⁵⁵ In addition, they may contribute to the formation of a pre-metastatic niche in bone by secreting chemoattractants such as CXCL12, facilitating the recruitment of CXCR4-expressing cancer cells to the bone marrow. These pro-metastatic processes are further supported by CAF-driven stromal stiffening (e.g., via LOXL2) and metabolic coupling (e.g., lactate shuttle).^{14,56} The biological functions of CAFs pose significant challenges for nanomedicine delivery. First, by promoting aberrant, leaky vasculature, they can cause heterogeneous nanoparticle distribution and loss via the EPR paradox.⁵⁷ Second, the dense, remodeled ECM and CAF-induced stromal stiffening create substantial physical barriers that limit nanoparticle penetration, especially in regions like nerve bundles and the bone marrow.^{58–60} Third, the lactate-rich, acidic microenvironment generated by CAF activity can inhibit therapeutic chemical reactions, such as the Fenton reaction, thereby reducing the efficacy of certain nanotherapeutic strategies.³⁷ Thus, through their multifaceted interactions within the TME, CAFs are pivotal in constructing an integrated network that dysregulates molecular signaling, facilitates pro-tumoral cell-cell crosstalk, remodels physical architecture, and reprograms metabolic pathways. This network fundamentally underpins the aggressive phenotype, therapy resistance, and immune evasion characteristic of advanced PCa.

Targetable Molecules and Pathways in CAFs

CAFs and the ECM they remodel present multiple potential targets for PCa therapy. However, it is important to distinguish molecular targets supported by PCa-specific evidence from those primarily extrapolated from other solid tumor models. Key targets include FAP, a molecule specifically and highly expressed on activated CAFs.⁶¹ Importantly, PCa-specific transcriptomic and immunohistochemical datasets consistently confirm stromal enrichment of FAP, supporting its relevance in the prostate tumor microenvironment rather than relying solely on cross-cancer observations. This distinct stromal expression profile highlights its translational potential for targeted therapeutics and intraoperative imaging probes.^{62,63} PDGFR β is predominantly expressed in α -SMA+/FAP+ CAF subsets and vascular smooth muscle cells. Its expression levels correlate positively with high Gleason scores, increased tumor volume, and elevated microvessel density.³⁸ These associations have been reported in prostate-specific tissue microarrays and TCGA-PRAD analyses, strengthening the disease-context relevance of PDGFR β targeting in PCa. Integrin α 11 (encoded by ITGA11) shows high and specific expression in certain CAF subpopulations. Critically, ITGA11 protein is barely detectable in normal adult tissues. Furthermore, Itga11-knockout mice exhibit no overt abnormalities in cardiac, pulmonary, or hepatic function.⁶⁴ Notably, ITGA11 upregulation has been demonstrated in PCa stromal compartments using both bulk and single-cell transcriptomic analyses, although functional validation in PCa-specific *in vivo* models remains limited. This expression pattern, together with preliminary safety observations, enhances its appeal as a candidate translational target. In contrast, some targets frequently used for CAF-directed nanomedicine delivery—such as α v β 3 integrin—are not specific to PCa and are broadly expressed in activated fibroblasts, angiogenic endothelium, and certain tumor cells across

multiple malignancies.^{65,66} Therefore, the application of $\alpha\text{v}\beta 3$ -targeted systems to PCa is largely supported by general tumor-stroma biology rather than prostate-restricted expression data. While integrin-targeted nanoparticles may still be effective in PCa due to shared stromal activation pathways, their rationale is based on conserved CAF phenotypes rather than PCa-specific molecular exclusivity.^{67,68}

Components of the CAF-remodeled ECM also represent potential targets. These include specific collagens (e.g., COL1A1), lysyl oxidase (LOX)—which cross-links collagen and contributes to stromal stiffness—and extra domain-A-containing fibronectin (EDA-FN). Their overexpression in tumor-associated stroma has been associated with aggressive disease behavior in PCa cohorts.^{69–72} However, it should be noted that many of these ECM alterations are also observed in other desmoplastic tumors, and therefore represent shared stromal remodeling signatures rather than prostate-exclusive features. A potential therapeutic advantage of certain stromal targets lies in their relatively restricted or condition-dependent expression in normal adult tissues, which may create a therapeutic window. Nonetheless, the degree of tumor selectivity varies among targets, and careful evaluation of on-target, off-tumor effects remains essential.^{73–75} For example, systemic inhibition of essential ECM components such as collagen, or direct targeting of widely expressed cytoskeletal proteins like α -SMA, could lead to unintended toxicity.^{74,76} Accordingly, strategies to mitigate these risks—such as locoregional delivery systems, tumor microenvironment-responsive prodrugs, or selective stromal reprogramming approaches—are being explored. The major targetable molecules and pathways associated with CAFs and the tumor ECM are summarized in Table 3.

The progression and therapeutic resistance of PCa are strongly linked to the activity of CAFs. CAFs support tumor progression through the release of diverse secretory factors and the activation of complex signaling networks. Cancer cells, through factors like TGF- β , activate CAFs, which in turn promote tumor malignancy via paracrine signaling across multiple pathways. For instance, CAF-secreted CXCL12 guides cancer cell chemotaxis and invasion via the CXCR4 axis. Furthermore, CXCL12 can establish a chemokine gradient that acts as a chemical barrier, inhibiting T-cell infiltration and contributing to immune evasion. Aberrantly activated FGF signaling (e.g., via FGF7) directly drives cancer cell proliferation and stimulates tumor angiogenesis. Therapeutic interventions, notably ADT, can remodel AR signaling within CAFs, altering their molecular profile. Through the secretion of factors like MMP11, these CAFs contribute to the development of CRPC, thereby driving both disease progression and therapy resistance. Moreover, CAFs derived from ADT-sensitive versus ADT-resistant tumors exhibit distinct molecular signatures, underscoring the pivotal role of AR signaling in defining CAF phenotype.^{88,89} Additionally, CAF-derived CXCL14 can polarize macrophages toward an immunosuppressive M2 phenotype via NF- κ B pathway activation, further shaping an immunosuppressive TME.⁹⁰ Direct contact between CAFs and cancer cells leads to the synergistic upregulation of Follistatin (FST). FST promotes cancer cell migration, proliferation, and *in vivo* tumorigenesis by antagonizing Activin A signaling. In nude mouse models, FST knockdown in cancer cells alone significantly inhibits tumor growth. However, effective suppression of cancer cell migration and proliferation requires concurrent FST knockdown in both cancer cells and CAFs.⁹¹ Furthermore, CAFs actively shape an immunosuppressive TME through the expression and secretion of immune-modulatory molecules, contributing to immunotherapy resistance. TGF- β , a key CAF-secreted immunosuppressant, directly inhibits T-cell activation and proliferation while promoting the differentiation and function of Tregs. IL-6, another CAF-derived factor, promotes an immunosuppressive milieu via STAT3 activation and is linked to myeloid-derived suppressor cell (MDSC)-mediated immune evasion and metastasis. Additionally, CAF-derived CXCL12 binds to CXCR4, physically excluding T cells while recruiting immunosuppressive cells like MDSCs, thereby enhancing immunosuppression.⁹² CAFs can also directly suppress immune cell function by expressing immune checkpoint molecules. For example, they can upregulate PD-L1 expression on both tumor and immune cells, thereby blunting the efficacy of PD-1/PD-L1 blockade therapy.³² Within the realm of immunometabolism, CAFs regulate CD73, an ectoenzyme that converts immunostimulatory extracellular ATP into immunosuppressive adenosine. This adenosine then signals through A2A receptors on immune cells (e.g., T cells), potently suppressing their anti-tumor activity.⁹³ CAFs may also express indoleamine 2,3-dioxygenase (IDO), indirectly inhibiting T-cell function and promoting Treg differentiation.⁹⁴ Nanomaterials offer a promising multifunctional platform to counteract CAF-mediated immunosuppression. Their core advantages—targeted delivery, capacity for combination therapy, and reduced systemic toxicity—make them attractive therapeutic candidates. Nanocarriers can be engineered to co-deliver CAF-targeting agents

Table 3 Targets on CAFs and ECM

Targets on CAFs and ECM	Target	Expression Specificity	Expression Profile	Safety	References
Target points on CAFs	FAP	Selectively and highly expressed on activated CAFs; barely detectable in normal prostate glands, smooth muscle, or vascular endothelium; further upregulated in bone metastases.	In TCGA-PRAD, the mRNA of FAP is significantly upregulated, while it is extremely low in GTEx normal prostate tissue; all CCLE PCa cell lines (LNCaP, VCaP, PC-3) show low or undetectable expression.	Normal tissues (pancreas, liver, lung, heart) barely express it	[62,77]
	PDGFR β	Primarily expressed on α -SMA ⁺ /FAP ⁺ CAFs and peritumoral vascular smooth muscle cells; very low in epithelial/immune cells and endothelium.	More than 300 PCa tissue microarrays show that 34% of the tumor stroma is PDGFR β -positive, and this is positively correlated with Gleason score ≥ 8 , tumor volume, and vascular density; in TCGA-PRAD, PDGFR β mRNA is significantly associated with high Gleason score and advanced stage.	It is expressed at low levels in normal prostate fibromuscular layer and vascular smooth muscle	[38]
	Integrin $\alpha 11$	Highly and specifically expressed on CAFs, particularly in collagen I-rich stromal areas; co-expressed with COL11A1 and COL1A1 in ECM-remodeling CAF subsets as revealed by single-cell RNA sequencing. In contrast, expression is nearly absent in normal prostate epithelium and smooth muscle, and only minimally detected in collagen-rich niches of adult tissues such as heart and lung, underscoring its tumor-restricted expression pattern and potential as a safe therapeutic target.	Single-cell/transcriptomic analysis reveals that ITGA11 is co-expressed with COL11A1 and COL1A1, marking specific CAF subpopulations; in TCGA-PRAD, the mRNA of ITGA11 is significantly upregulated in the ISUP 3–5 group ($\log_2FC \approx 1.2$, $P < 0.01$); expression in CCLE PCa cell lines (LNCaP, VCaP, PC-3) is below the detection threshold.	ITGA11 protein is extremely low in normal tissues; animal knockout studies have not shown abnormalities in heart, lung, and liver function	[38,64,78,79]
	α -SMA	Canonical CAF activation marker; constitutively expressed in normal prostate smooth muscle; absent in glandular epithelium.	Tissue microarrays ($n \approx 120$) revealed a significantly elevated proportion of α -SMA ⁺ CAFs in the PCa stroma (approximately 41%), correlating with tumor aggressiveness; α -SMA expression was extremely low in CCLE PCa cell lines, and was only detected in fibroblast cell lines	Widely expressed in normal smooth muscle (prostate, vascular). Direct targeting (ADC) risks on-target off-tumor vascular toxicity (preclinical evidence). Stromal reprogramming preferred over ablation.	[14]

Target points on ECM	Collagen I / III	The distribution pattern is the same in both cancerous and normal tissues, with no tumor-specific localization.	Collagen I shows an upward trend in expression in PC, but without statistical significance. It shows no significant association with tumor aggressiveness (Gleason score). In contrast, Collagen III expression is significantly higher in PC than in normal tissue, making it a more distinct marker of cancer-associated stromal remodeling.	Collagen I exhibits high basal expression in normal tissues. Consequently, targeted therapies carry a high potential for off-target effects, which may disrupt normal stromal architecture and function. Similarly, Collagen III is also present in normal tissues and is upregulated in PC. Targeting it similarly entails a high risk of off-target toxicity.	[80]
	LOX	Responsible for collagen/elastic fiber cross-linking, enhancing matrix rigidity; upregulated in CAF, promoting sclerosis; low expression in normal prostate epithelium	IHC exhibits moderate intensity in prostate tumor epithelium and significantly increases in bone metastasis samples; non-malignant prostate epithelium shows low or negative LOX expression, and LOX mRNA in TCGA-PRAD is associated with Gleason and metastasis	Normal tissues (lung, blood vessels, skin) all express LOX	[38]
	EDA-FN	Oncofetal variant of cellular fibronectin; highly expressed in activated fibroblasts/myofibroblasts in fibrotic stroma and tumor microenvironment (invasive front). Co-localizes with α -SMA ⁺ myofibroblasts in fibroblastic foci. In PCa, enriched in CAF-rich stromal areas; virtually absent in normal adult tissues except transient wound healing.	EDA-FN expression is markedly upregulated in IPF-derived lung fibroblasts at both protein and transcript levels, correlating with increased α -SMA expression and an approximately 1.5-fold rise in the EDA inclusion ratio of fibronectin transcripts; functionally, EDA ^{-/-} mice are protected from bleomycin-induced pulmonary fibrosis, exhibiting reduced collagen deposition and diminished α -SMA ⁺ myofibroblast accumulation; mechanistically, EDA-FN is required for TGF- β activation and subsequent TGF- β -induced upregulation of α -SMA and collagen I.	Normal tissues express it transiently during the embryonic stage or wound healing, and the expression level is extremely low in adult tissues	[81]
	MMP-2 / MMP-9	Secreted by multiple cell types in TME, including CAFs, tumor-associated macrophages (TAMs), and tumor cells themselves. MMP9 expression correlates positively with infiltration of TAMs, Tregs, neutrophils, and dendritic cells in multiple cancers. In PCa, MMP9 is upregulated in tumor tissues and associated with aggressive features	In pan-cancer analyses, MMP9 mRNA is significantly upregulated across 28 tumor types, with concordant protein overexpression confirmed by CPTAC and immunohistochemistry in multiple malignancies; clinically, high MMP9 expression correlates with poor overall and disease-specific survival in several cancers, including bladder, liver, kidney, and glioblastoma; immunologically, MMP9 positively associates with infiltration of diverse immune cell populations and expression of immune checkpoint molecules such as PD-L1 and CTLA-4; furthermore, single-cell analysis in breast cancer reveals that MMP9 expression aligns with functional states related to inflammation, proliferation, hypoxia, and cell cycle progression.	MMP plays a physiological role in embryonic development and wound healing; currently, there is a preference for using tumor enzyme-activated prodrugs or locally delivered MMP inhibitors to reduce systemic toxicity	[14,82,83]

(Continued)

Table 3 (Continued).

Targets on CAFs and ECM	Target	Expression Specificity	Expression Profile	Safety	References
	Hyaluronic acid (HA)	HA is 3–8 times higher in the stroma of PCa compared to normal prostate tissue, and is even higher in high Gleason and metastatic samples; it is ubiquitous in normal tissues (skin, cartilage, vitreous humor of the eye) but at low levels	The abnormal metabolism and degradation products (low molecular weight HA) of HA in the TME promote inflammation and immunosuppression	Systemic inhibition of hyaluronic acid synthesis (eg, HAS inhibitors) or enzymatic depletion (eg, PEGPH20) is feasible. However, these approaches may impair wound healing and disrupt tissue homeostasis. Hyaluronic acid is biocompatible, biodegradable, and FDA-approved. Hyaluronic acid-modified nanocarriers (e.g., CHA nanoparticles) enable CD44-mediated active targeting. This strategy achieves tumor-selective delivery with minimal off-tumor toxicity.	[83,84]
	FNI	CAF-derived ECM glycoprotein; highly enriched in PCa stroma. Soluble FNI present in plasma; tissue isoform low in normal adult tissues.	The mRNA expression of FNI is significantly upregulated in TCGA-PRAD ($\log_2FC \approx 1.0$, $P < 0.001$)	FNI is a plasma protein, and systemic inhibition can affect platelet aggregation and wound healing; currently, there is a preference for utilizing its Arginine-Glycine-Aspartic Acid (RGD) domain for drug delivery rather than direct inhibition	[38,85,86]
	Tenascin-C (TNC)	TNC is highly expressed in the PCa stroma (especially in the bone metastasis microenvironment), promoting cell adhesion and migration; it is almost undetectable in normal prostate tissue	TNC is significantly expressed in the bone metastatic sites of PCa and is associated with poor prognosis	In normal tissues, TNC expression is extremely low, only appearing during embryogenesis and wound repair stages	[38,87]

Notes: TCGA-PRAD represents bulk RNA-seq from mixed tumor–stroma tissues; cell type–specific expression cannot be fully resolved without deconvolution. CCLE data are derived from in vitro prostate cancer cell lines lacking stromal compartments; low expression does not exclude CAF/ECM enrichment in vivo. scRNA-seq evidence (human or mouse as cited) depends on clustering/annotation and may vary across platforms and analytical pipelines; subtype labels reflect transcriptional states rather than fixed lineages. Clinicopathologic associations are largely correlative, and many mechanistic/safety inferences are based on preclinical models.

alongside immune checkpoint inhibitors. For instance, pH-responsive calcium carbonate NPs have been designed to co-load anti-PD-L1 antibodies and the CD73 inhibitor adenosine 5'-(α,β -methylene)diphosphate (APCP). This strategy enables dual immune activation by concurrently blocking the PD-1/PD-L1 axis and the CD73-adenosine pathway. Leveraging the tumor-targeting and acid-responsive properties of the NPs, it enhances therapeutic efficacy while reducing the required antibody dose by 20-fold and minimizing systemic immune-related adverse effects. This approach has demonstrated efficacy in overcoming CAF-mediated immune resistance and holds significant potential for reducing systemic toxicity. Future research should prioritize the development of models that more accurately recapitulate human CAF heterogeneity and advance the clinical translation of such multifunctional nanoplateforms for refractory cancers, including PCa.⁹³

Classification and Application of Nanomaterials for PCa

Types of Nanomaterials

The clinical translation of promising natural compounds for PCa therapy, such as resveratrol (RSV), genistein, and curcumin (CUR), is hindered by inherent pharmacological challenges. These agents frequently suffer from poor aqueous solubility, low bioavailability, chemical instability, and limited cellular uptake, which can compromise their efficacy and contribute to drug resistance. Nanotechnology offers a powerful strategy to overcome these limitations. Engineered nanomaterials enable precise targeting, efficient drug loading and controlled release, enhanced cytotoxic delivery, and synergistic combination therapies designed to overcome resistance mechanisms.⁹⁵ Specifically, nanomaterials can be surface-functionalized to target CAFs selectively. This allows for the targeted delivery of diverse payloads—including chemotherapeutics, genetic material, or immunomodulators—to remodel the TME and improve treatment outcomes. A wide array of nanomaterial classes has been explored as drug delivery vehicles for PCa. These include inorganic nanomaterials (e.g., TE-@MS-x, TO-@MS-x), organic NPs (e.g., DTX-SLN-Anis, PSMA-2DG-D), carbon-based nanomaterials (e.g., HexakisaminoC₆₀), and composite/hybrid nanomaterials (such as DCM@GDY-CuMOF@DOX). Each class possesses distinct physicochemical properties tailored for specific therapeutic cargoes, making nanomaterials indispensable components in the development of novel PCa therapies. A detailed summary of these nanomaterial classes and representative examples is provided in Table 4.

Inorganic nanomaterials, such as TE-@MS-x and TO-@MS-x, are utilized in nanomedicine for their high specific surface area, which results from a large pore volume and hydrophilic surface. This property significantly enhances their loading capacity for drug molecules. For instance, when loaded with doxorubicin (DOX) under alkaline conditions (pH 11), these materials achieved capacities of 425 $\mu\text{g mg}^{-1}$ and 481 $\mu\text{g mg}^{-1}$, surpassing the 347 $\mu\text{g mg}^{-1}$ capacity of conventional mesoporous silica nanoparticles (MSNs). However, as silicon-based materials, they exhibit relatively slow in vivo degradation. Their long-term biocompatibility and clearance pathways thus require further investigation.⁹⁶ Another class of inorganic nanomaterials, superparamagnetic iron oxide nanoparticles (SPIONs), demonstrate excellent heat generation under alternating magnetic fields, enabling effective tumor cell ablation in magnetic hyperthermia therapy. A key challenge is their potential for nonspecific accumulation. Surface modifications, like polyethylene glycol (PEG) conjugation (PEGylation), are often employed to reduce opsonization and minimize immune recognition, thereby improving their pharmacokinetic profile.⁹⁷ In summary, inorganic nanomaterials offer unique physicochemical properties suitable for diverse applications, including high drug loading, photothermal therapy (PTT), and cytotoxicity. However, challenges related to biocompatibility, controlled degradation, clearance, and potential toxicity must be addressed for successful clinical translation. Organic nanomaterials generally offer favorable biocompatibility and biodegradability. For example, the PSMA-targeted nanoparticle PSMA-2DG-D facilitates specific endocytosis by PSMA-expressing cancer cells.^{107,108} While in vivo imaging confirms effective tumor enrichment and minimal off-target accumulation, its efficacy is inherently limited to PSMA-positive populations. Tumor heterogeneity resulting in low or absent PSMA expression can thus compromise therapeutic outcomes. Other organic platforms, such as StarPEG nanocarriers and DNA-PS@MIL-101, often depend on specific pathological cues (e.g., enzyme activity, redox potential) for triggered drug release.^{101,103} To overcome reliance on single stimuli, innovative designs are emerging. Wang et al developed a pH- and H₂O₂-dual-responsive conductive polymer nanoparticle.¹⁰⁹ This system integrates multiple triggers—including pH, glutathione

Table 4 Classification of Nanomaterials and Their Functions

Type	Material	Subtype	Size	Drug type	Target	References
Inorganic nanomaterials	TE-@MS-x / TO-@MS-x	Mesoporous silica NPs	270-320 nm	Doxorubicin	Passive targeting	[96]
	Superparamagnetic iron NPs	Iron oxide NPs	59-85nm	-	Passive targeting	[97]
	PSMA-targeted GNPs	Gold NPs	About 17.1 nm	-	PSMA	[98]
Organic nanomaterials	DTX-SLN-Anis	Solid lipid NPs	174 ± 9.1 nm	Docetaxel	Sigma receptor	[99]
	PSMA-2DG-D	Dendrimer	About 4–5 nm	Cabozantinib	PSMA-positive PCa cells	[100]
	DNA-PS@MIL-101	Metal-organic framework	80-120 nm	Photosensitizer	Passive targeting (specific killing capability derived from hydrogen peroxide activation in the TME)	[101]
	Polyacrylic acid nanogel	Nanogel	250NGBD: 67 ± 5 nm 450NGBD: 124 ± 16 nm	Radionuclides (such as beta emitters yttrium-90 and lutetium-177)	Gastrin-releasing peptide receptor	[102]
	StarPEG nanocarrier	Star-shaped polymer nanocarrier	About 12 nm	Radioactive isotope ¹⁷⁷ Lu (lutetium-177)	PSMA	[103]
Composite nanomaterials	Lpo@MnS-GOx NPs	Enzyme/inorganic nanocomposite	About 150 nm	-	Human PCa cells (PC-3 cell line)	[104]
	DCM@GDY-CuMOF@DOX	Metal-organic framework/graphdiyne composite	280.5 nm	Adramycin, copper ion	DUI45 PCa cell membrane	[105]
Carbon-based nanomaterials	HexakisaminoC ₆₀	Fullerene derivatives	100 nm	Small Interfering RNA (siRNA)	Human PCa cells expressing GFP protein	[106]
	JK39	Peptide/protein nanomaterials	Two sub-population aggregates: approximately 134 nm and 599 nm	siRNA	Human PCa cells expressing GFP protein	[106]

(GSH) levels, and enzyme activity—to achieve more precise drug or photosensitizer release, thereby reducing dependency on any single factor concentration. Composite or hybrid nanomaterials integrate components to achieve synergistic effects. For instance, Lpo@MnS-GOx NPs have demonstrated high efficacy against CRPC, significantly inhibiting tumor growth in both cellular and animal models.¹⁰⁴ Similarly, DCM@GDY-CuMOF@DOX employs a cancer cell membrane coating (derived from DU145 cells) to confer homologous targeting, markedly enhancing its uptake by PCa cells.¹⁰⁵ While demonstrating promising safety profiles, composite nanomaterials often involve complex synthesis and raise concerns about potential metal ion leakage. Strategies to mitigate these challenges include streamlining synthesis through continuous-flow processes to reduce procedural steps, batch variability, and production time; encapsulating metal cores with high-stability macrocyclic ligands; applying secondary protective barriers, such as carbon shells, polyethylene glycol coatings, or biodegradable polymer layers; and, when appropriate, co-administering systemic chelators as part of a multilayer protection strategy. Carbon-based nanomaterials possess a high specific surface area, tunable surface chemistry, distinctive optoelectronic properties, and robust mechanical strength. These properties provide substantial versatility for biomedical applications, including drug and gene delivery, photothermal and photodynamic therapy, precision imaging, and tissue engineering.¹¹⁰ For example, HexakisaminoC₆₀ serves as a non-toxic photosensitizer for PDT.¹⁰⁶ Its derivative, JK39, incorporates D-glucosamine groups onto the hexa-amino scaffold. These modifications foster hydrogen bonding and carbohydrate-nucleic acid interactions, which help stabilize siRNA. With a high positive zeta potential (exceeding +54 mV), JK39 forms complexes that provide effective charge shielding and significantly protect siRNA from enzymatic degradation *in vitro*. Strategies for nanotechnology-based targeting and modulation of CAFs are illustrated in Figure 3.

In addition, liposomes, as a widely studied nanocarrier in the treatment and detection of PCa, have a lipid bilayer composition and structure similar to mammalian cell membranes, which helps to enhance targeting and uptake efficiency towards PCa cells. Radioactive labeled NPs such as gold NPs (AuNPs) have been developed for imaging and treatment of PCa. For example, the functionalized gold NPs (198AuNPs EGCg) developed by Shukla et al have shown significant tumor retention and therapeutic effects in *in vivo* studies, effectively inhibiting tumor growth. In addition, polymer nanocarriers belonging to organic nanomaterials such as PEG NPs can enhance drug delivery efficiency by targeting PSMA ligands (such as ACUPA). The PEG nanocarrier designed by Meher et al demonstrated good tumor penetration and retention ability in animal models.¹¹¹ In terms of immunotherapy, spherical nucleic acid (SNA) nanovaccines are used for PCa treatment by targeting dendritic cells (DCs) and enhancing antigen presentation, which can activate T cell immune responses and increase cytokine secretion. However, the stability, biocompatibility, and *in vivo* clearance rate of nanomaterials remain current challenges that require further optimization to enhance their clinical application potential.¹¹²

CAF-Targeted Modification Strategies

CAFs are dominant stromal components that drive tumor progression through multiple mechanisms, including cytokine secretion, ECM remodeling, and suppression of immune cell infiltration. Functionalizing nanomaterials with ligands that specifically recognize CAF surface markers enables the precise delivery of therapeutic or diagnostic payloads to CAFs. This targeted approach can disrupt pro-tumoral CAF functions or induce their reprogramming, ultimately improving intratumoral drug penetration, reducing systemic toxicity, and enhancing the efficacy of immunotherapies.¹¹³ This section outlines five principal strategies for achieving CAF-targeted modification, which are summarized as follows.

Antibodies and Antibody Fragments (Anti-FAP)

Whole antibodies or functional fragments that specifically recognize CAF surface markers can serve as targeting moieties to direct nanocarriers to CAFs. This enables anti-FAP ligands on the nanocarrier surface to bind specifically to FAP proteins on CAFs. Subsequently, receptor-mediated endocytosis internalizes the nanocarrier and its payload into CAFs, facilitating precise drug release.¹¹⁴ For example, the LeBeau team successfully targeted FAP using shark-derived single-domain antibodies (VNARs). Selected VNARs (e.g., H4) exhibit picomolar affinity and are rapidly internalized into FAP-positive cells without inhibiting enzymatic activity. These VNARs can be engineered as Fc fusion proteins for multiple applications, including conjugation to monomethyl auristatin E (MMAE) to generate antibody–drug conjugates

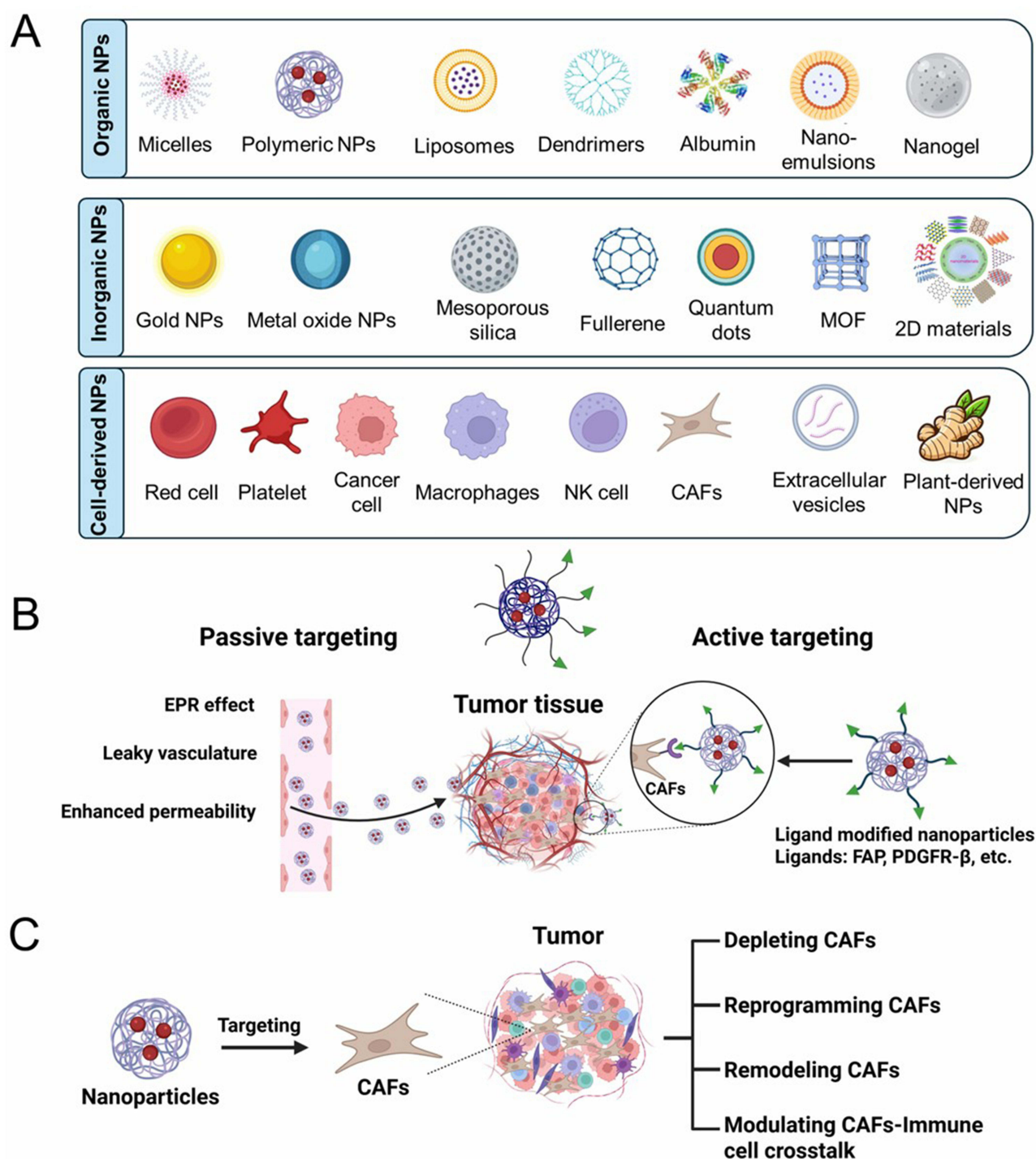


Figure 3 (A) NPs are classified according to their constituent components. (B) Passive and active targeting of CAFs through nanotechnology strategies. (C) Modulation of CAFs by NPs. Reproduced from,³² Copyright © 2025 by authors.

(ADCs) that target and eliminate FAP-positive cells, as well as radiolabeling for positron emission tomography (PET) imaging. Together, these capabilities support a theranostic strategy that integrates targeted therapy with molecular imaging.^{115,116} Alternatively, engineered protein nanocages offer another targeting strategy. Researchers have conjugated the Fab fragment of an anti-FAP antibody to H-ferritin (HFn) nanocages using PEG linkers. This design enhances the binding of nanocages to cells with high FAP expression while reducing nonspecific uptake, thereby achieving precise targeting. Experiments demonstrated that functionalized nanocages (HNav-FAP) exhibit enhanced cytotoxicity and

higher drug uptake in both cellular and animal models.¹¹³ Furthermore, fully human monoclonal antibodies and their derivatives represent another important technological avenue. Fully human anti-FAP antibodies can be generated using phage display libraries, transgenic mice, or single-cell B-cell sequencing, with their binding affinity further optimized through affinity maturation.¹¹⁷ These antibodies exhibit high affinity and long half-lives, making them suitable for ADC development. Additionally, single-chain variable fragments (scFvs) derived from these antibodies exhibit superior tumor penetration due to their low molecular weight, making them ideal for constructing chimeric antigen receptor T (CAR-T) cells and molecular imaging probes. In summary, selecting high-affinity anti-FAP binding units is a rational design process guided by the intended application. Whether whole antibodies or smaller fragments, the core binding units are initially screened using advanced display technologies and then optimized via *in vitro* evolution and protein engineering, ultimately yielding molecules tailored for specific therapeutic or diagnostic purposes.

Peptides and Aptamers

Short peptides or single-stranded nucleic acid aptamers can target CAFs. For instance, SPARC (secreted protein acidic and rich in cysteine) is a glycoprotein highly expressed and secreted by CAFs into the ECM. Like antibodies, these targeting molecules can induce endocytosis via ligand-receptor binding. FAP is overexpressed in over 90% of epithelial-derived tumor stroma but shows minimal expression in normal tissues, making it an ideal target. Consequently, FAP-targeted nanomaterials hold significant potential for tumor diagnosis and therapy. In PCa and oral squamous cell carcinoma, FAP expression is primarily localized to tumor-associated fibroblasts and perivascular regions. To target FAP, the Dmochowska team synthesized block copolymers via reversible addition-fragmentation chain-transfer (RAFT) polymerization. They then conjugated an optimized small-molecule FAP ligand to the polymer chain terminus and coated iron oxide NPs to construct a targeted magnetic resonance imaging(MRI) contrast agent.¹¹⁸ Alternatively, the Li team functionalized PEG-coated nano-graphene oxide with FAP-recognition peptides via π - π stacking, creating a nanosystem that combines chemotherapy and PTT. Experimental results indicate that both strategies exhibit high specificity. *In vitro* studies confirmed that FAP-targeted nanomaterials are internalized more efficiently by tumor cells expressing the target. Animal studies further validated the targeting efficacy: in PCa models, FAP-targeted NPs provided better tumor delineation than PSMA-targeting agents;¹¹⁹ in oral squamous cell carcinoma models, the FAP-targeting system showed specific tumor accumulation.

Small Molecule and Carbohydrate Ligands

Small-molecule FAP inhibitors (FAPIs) have been developed as high-affinity ligands that bind to the FAP catalytic domain with nanomolar affinity.¹²⁰ Conjugating FAPI ligands to nanocarriers via click chemistry enables the construction of FAP-targeted NPs, such as those based on iron oxide or lutetium-177 oxide ($^{177}\text{Lu}_2\text{O}_3$). These FAP-targeted NPs demonstrate superior contrast enhancement in MRI of PCa compared to PSMA-targeting strategies, alongside favorable tumor penetration and retention profiles.¹²¹ Furthermore, the clinical utility of FAPI for molecular imaging is exemplified by probes like [^{18}F]AlF-NOTA-FAPI-04. This PET/CT tracer shows high tumor accumulation in patients, validating its targeting efficiency and highlighting its potential for theranostic applications.¹²² Preclinical studies indicate that these FAP-targeted NPs exhibit a favorable safety profile with no significant off-target tissue toxicity observed *in vivo*.¹²¹ Beyond small molecules, carbohydrate-based ligands such as HA are widely exploited to target the CD44 receptor, which is commonly overexpressed on both CAFs and cancer cells. Electrostatic interactions between negatively charged HA and positively charged chitosan drive the spontaneous self-assembly of chitosan-hyaluronic acid Nanoparticles (CHA NPs). This nanoplateform exhibits pH-responsive drug release and is efficiently internalized by CD44-high cells via HA-mediated active targeting. This mechanism significantly enhances cellular uptake and anticancer efficacy, as demonstrated in breast cancer, lung cancer, and other tumor models.¹²³ In summary, surface functionalization of nanomaterials with FAPI small molecules or HA polysaccharides represents two experimentally validated and effective strategies for targeting both CAFs and the broader TME.

pH- and Enzyme-Responsive Groups

pH-responsive designs are incorporated into nanocarriers to exploit the mildly acidic tumor extracellular microenvironment (pH ~6.5–6.8) and the more acidic lysosomal compartments (pH ~5.0–6.0). For instance, in an NPF@DOX system,

an acidic pH accelerates doxorubicin release by disrupting hydrogen bonds and π - π stacking interactions. In contrast, release is minimal at neutral pH (7.4), enabling precise, pH-triggered drug control.¹¹⁹ Similarly, in peptide-based nanocarriers, histidine residues serve as pH-responsive switches. Protonation under acidic conditions triggers a shift in peptide secondary structure from β -sheet/antiparallel β -sheet to a random coil, resulting in nanoparticle disassembly and the release of nucleic acid payloads for efficient gene delivery.¹²⁴ Furthermore, cyclic peptide-polymer conjugates leverage the protonation/deprotonation of tertiary amine-based polymers (e.g., poly(DMAEMA) or poly(DEAEMA)) to control the pH-dependent self-assembly and disassembly of nanotube structures, thereby refining stimulus-responsive drug delivery.¹²⁵ These pH-responsive strategies hold translational potential for PCa, which is characterized by an acidic TME and CAF enrichment. However, their efficacy requires further validation in relevant *in vivo* models (Figure 4).

Nanomedicine Strategies Targeting CAFs

Nanotherapeutic strategies targeting CAFs have emerged as a key innovative approach in the precision medicine landscape for PCa. By reshaping the TME, these strategies aim to inhibit the tumor-promoting functions of CAFs, thereby enhancing therapeutic efficacy.¹²⁶ These approaches primarily use functionalized nanocarriers, such as liposomes, polymeric nanoparticles, and inorganic nanomaterials, to target CAF-associated markers, for example FAP. The nanocarriers deliver payloads such as chemotherapeutic agents, siRNA, or immunomodulators to inhibit CAF activation, reduce the secretion of tumor-promoting factors, and counteract therapy resistance and metastatic potential.³⁷ Recent studies indicate that nanomedicine-based combination therapies can synergize with conventional treatments to enhance anti-tumor efficacy. Furthermore, by integrating with immunotherapy, they can activate anti-tumor immune responses, offering a promising translational pathway for PCa management. This section systematically explores the design principles, mechanisms of action, and application prospects of CAF-targeted nanotherapeutic strategies, aiming to provide a theoretical framework for advancing PCa theranostics (Figure 5).

CAF Ablation and Inhibition Strategies

Nanomaterials can achieve precise targeting and functional inhibition of CAFs through diverse mechanisms. A core strategy is active targeted ablation, which exploits specific proteins overexpressed on the CAF surface. For example, one study engineered ferritin nanocage-based NPs (α -Fe₂O₃) loaded with the photosensitizer zinc phthalocyanine (ZnF₁₆Pc) and conjugated to an anti-FAP single-chain antibody (designated FAP-Z@FRT). Following intravenous injection, this system specifically accumulates in the tumor stroma. Upon local red-light irradiation, it generates cytotoxicROS via PDT, effectively ablating FAP-positive CAFs.¹²⁷ This approach has been shown to stimulate anti-tumor immunity and induce an abscopal effect, inhibiting the growth of non-irradiated, distant tumors. In PCa models, an alternative strategy employs pH-responsive, envelope-shaped NPs surface-modified with ACUPA ligands for specific targeting of PSMA. This nanoplatform efficiently delivers siRNA to the tumor site, silencing the expression of prohibitin-1 (PHB1)—a gene upregulated in both CAFs and cancer cells—and thereby inhibiting tumor growth.¹²⁸ Furthermore, conjugating FAP antibodies to nanocarriers like gold NPs or liposomes is a common strategy for direct CAF ablation, enabling targeted delivery of chemotherapeutics or PTT.⁶ A third strategy leverages external energy activation. For instance, liposomal NPs co-loaded with perfluoropentane (PFP) and chemotherapeutic agents can undergo a liquid-to-gas phase transition upon exposure to low-intensity focused ultrasound (LIFU). This phase transition triggers localized drug release and enhances cytotoxicity, providing a distinct pathway for CAF targeting.¹²⁹ However, a critical caveat is that complete eradication of CAFs carries significant risks.¹³⁰ This is due to the high functional heterogeneity inherent to CAFs. Studies of prostate tissues, from pre-cancerous lesions like proliferative inflammatory atrophy (PIA) to cancer, indicate that stromal FAP upregulation is part of a tissue repair response to chronic injury and inflammation. Consequently, certain CAF subpopulations likely contribute to maintaining tissue homeostasis. Therefore, indiscriminate ablation of CAFs can disrupt stromal structural support and normal repair functions. Preclinical models have demonstrated that such non-selective targeting can paradoxically enhance tumor invasiveness and accelerate metastasis.³² Therefore, the optimal nanomedicine strategy should aim for the selective ablation or functional reprogramming of specific tumor-promoting CAF subpopulations via precise targeting, rather than broad-spectrum clearance. This approach seeks to effectively reverse immunosuppression while preserving beneficial stromal functions and ensuring treatment safety.^{32,127,128}

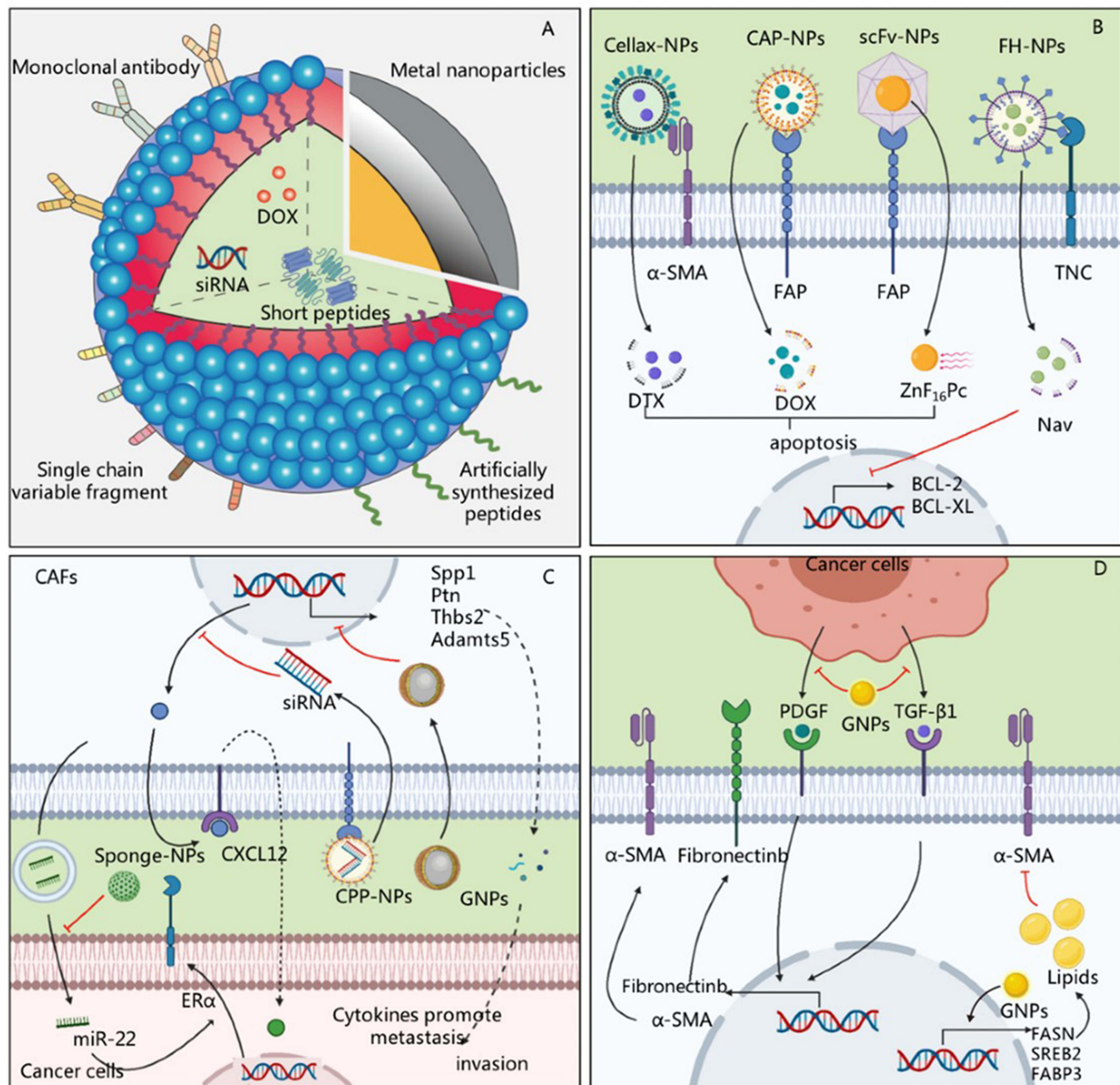


Figure 4 The nanomaterials targeting CAFs. **(A)** Illustration of the basic structure of nanosystems targeting CAFs. The nanosystems mainly consist of three parts: targeting ligands, drug-carrying systems, and cargo. Metal nanoparticles are mainly composed of metal particles with tiny sizes. **(B)** Targeting ligands including cellax, cleavable amphiphilic peptide (CAP), single-chain variable fragments (scFv), and FHKHKSPALPSVGGG (FH) in the nanoparticles specifically bind to α -smooth muscle actin (α -SMA), fibroblast-activated protein (FAP), and tenascin C (TNC) on the surface of CAFs to promote the entry of chemotherapeutic drugs, including doxorubicin (DOX) and docetaxel (DTX), or photosensitizers zinc hexafluorophthalocyanine (ZnF₁₆Pc), or short peptides navitoclax (Nav) into cells, and target the killing of CAFs or up-regulate the expression of BCL-2 and BCL-XL to increase the apoptosis of CAFs. **(C)** The sponge nanoparticles (sponge-NPs) neutralize miR-22 in the exosomes of CAFs, which inhibit the expression of estrogen receptor- α (ER- α) and reduce therapeutic resistance. The siRNA in CPP-NPs decrease the expression of C-X-C motif chemokine ligand 12 (CXCL12), subsequently reducing the cancer metastasis of tumor. Gold nanoparticles (GNPs) exhibit a suppressive role in tumor invasion, inhibiting expression of osteopontin (Spp1), pleiotrophin (Ptn), thrombospondin-2 (Tnbs2), and ADAM metalloproteinase with thrombospondin type 1 motif 5 (Adams5). **(D)** GNPs inhibit the expression of α -SMA and fibronectin in CAFs by inhibiting the platelet-derived growth factor (PDGF) and transforming growth factor- β 1 (TGF- β 1) expression in the cancer cells. It also induces the up-regulated expression of fatty acid synthesis genes in CAFs, including fatty acid synthetase (FASN), sterol regulatory element-binding protein 2 (SREBP2), and fatty acid-binding protein 3 (FABP3) genes, increases the lipid content, therefore inducing CAFs to stay in a quiescent state, and inhibits tumor-promoting functions. Back arrows: promotion; red "T" arrows: inhibition. Reproduced from,⁵⁴ Copyright © 2021 by authors.

CAF Reprogramming and Normalization Strategies

Nanotherapeutic strategies that specifically target and functionally reprogram CAFs can effectively reverse the immunosuppressive TME towards an immune-active state.¹²⁷ CAFs, the most abundant stromal cells in the TME, contribute to immunosuppression by secreting factors like CXCL12, which activates the STAT3 signaling pathway. This signaling not

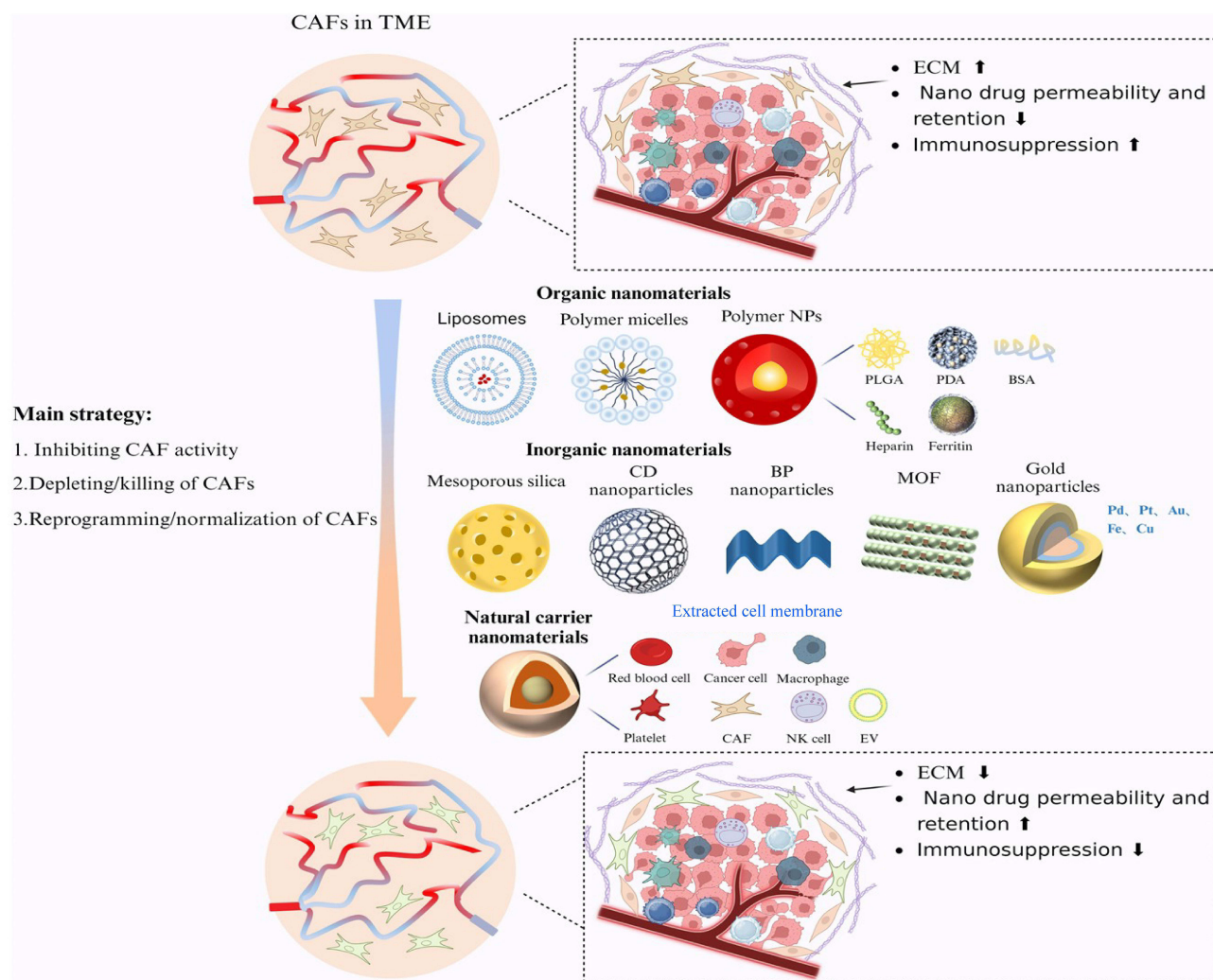


Figure 5 Schematic overview of nanomedicine strategies targeting cancer-associated fibroblasts (CAFs) to modulate the tumor microenvironment (TME). This schematic summarizes how CAF-rich TMEs can promote tumor progression by increasing extracellular matrix (ECM) deposition, reducing nanodrug permeability/retention, and enhancing immunosuppression, and illustrates representative nanomaterial classes used to counter these effects. The main CAF-directed strategies include inhibiting CAF activity, depleting or killing CAFs, and reprogramming or normalizing CAFs. Representative organic nanomaterials (liposomes, polymer micelles, polymer nanoparticles and polymer-derived carriers such as PLGA, PDA, BSA, heparin, ferritin), inorganic nanomaterials (mesoporous silica, carbon-based nanoparticles, black phosphorus nanoparticles, metal–organic frameworks, and gold nanoparticles), and natural carrier-based systems (cell membrane-derived biomimetic coatings from red blood cells, cancer cells, macrophages, platelets, CAFs, NK cells, and extracellular vesicles) are shown as platforms for CAF targeting and delivery. Symbols and graphical elements: In the dashed rectangular insets, upward arrows (↑) indicate an increase and downward arrows (↓) indicate a decrease in the listed features. The upper inset depicts CAF-driven changes (ECM ↑, nanodrug permeability and retention ↓, immunosuppression ↑), whereas the lower inset depicts the intended effects following CAF-targeted nanotherapy (ECM ↓, nanodrug permeability and retention ↑, immunosuppression ↓). Dotted/dashed boxes and dotted connector lines denote zoomed-in regions and conceptual links between the global CAF-rich microenvironment and the corresponding local tumor cross-section. Reproduced from,⁹² Copyright © 2025 by authors.

Abbreviations: CAF, cancer-associated fibroblast; TME, tumor microenvironment; ECM, extracellular matrix; NP, nanoparticle; PLGA, poly(lactic-co-glycolic acid); PDA, polydopamine; BSA, bovine serum albumin; CD, carbon dot; BP, black phosphorus; MOF, metal–organic framework; NK cell, natural killer cell; EV, extracellular vesicle.

only perpetuates CAF activation in an autocrine manner but also drives the transformation of normal fibroblasts into CAF-like cells.¹³¹ Furthermore, CAFs promote tumor progression by producing excessive ECM and recruiting immunosuppressive cells. To overcome these pro-tumorigenic functions, diverse nanomaterial-based reprogramming strategies have been developed. For example, Fei et al designed NPs co-loaded with retinoic acid (RA) and ferulic acid (GA) to target CAFs. This approach directly reversed CAF activation, induced tumor vascular normalization, and reduced ECM deposition.¹³² In a different approach, Li et al utilized dendritic nanomedicines to disrupt CAF amino acid metabolism, thereby functionally inhibiting their ECM synthesis capacity.¹³³ Similarly, Zhou et al employed ferritin NPs conjugated with anti-FAP single-chain antibodies for targeted PDT. This strategy enabled specific depletion of CAFs at the tumor site and, uniquely, stimulated antigen-specific anti-CAF cellular immunity, demonstrating protective potential across

multiple tumor types.¹²⁷ Collectively, these nanomaterial-mediated interventions disrupt the physical and biochemical barriers of the TME, significantly enhancing the penetration and accumulation of therapeutic agents within tumors. Importantly, CAF reprogramming was associated with tumor microenvironment remodeling, including reduced hypoxia and increased infiltration of effector immune cells such as CD8⁺ T cells and natural killer cells, along with decreased abundance of immunosuppressive populations including regulatory T cells and myeloid-derived suppressor cells.^{132,133} Ultimately, integrating such reprogrammed CAF-targeting nanoplateforms with immune checkpoint blockade or other immunotherapies can synergistically enhance anti-tumor immunity. This combination strategy potently inhibits both primary and distal tumor growth and has demonstrated favorable preclinical safety profiles, offering a powerful approach for achieving systemic tumor control.

Nanotargeted Strategies to Overcome CAF-Mediated ECM Barriers

The tumor ECM is a dense, cross-linked network composed of collagen, elastin, proteoglycans, glycosaminoglycans, and other components. This structure forms a major physical barrier that significantly impedes drug diffusion within the tumor stroma.¹³⁴ Consequently, strategies aimed at degrading ECM components or downregulating their expression have emerged as promising approaches to enhance the permeability and distribution of anticancer therapeutics. The hormone relaxin can degrade ECM components and upregulate MMP expression by binding to leucine-rich repeat-containing G protein-coupled receptors (LGRs) on tumor cells. This action has been shown to improve the distribution and intratumoral penetration of oncolytic adenoviruses.¹³⁵ However, the long-term impact of relaxin on tumor progression remains controversial, as it may also promote invasiveness in some contexts.¹³⁶ Alternatively, transiently opening or modifying tumor epithelial junctions can enhance drug penetration. For instance, the JO-1 peptide binds to and cleaves desmoglein-2 (DSG2), triggering an EMT-like signaling pathway that temporarily disrupts tumor epithelial junctions, thereby promoting drug penetration.¹³⁷ Another approach utilizes the iRGD peptide, which first binds to integrins (e.g., $\alpha\beta3/5$) on tumor vasculature. This binding exposes a C-end rule (CendR) motif that subsequently binds to neuropilin-1 (NRP-1), triggering a bulk transcytosis pathway. This process facilitates the selective accumulation and enhanced tissue penetration of co-administered drugs or NPs. Beyond direct ECM degradation, innovative nanomedicine design is crucial for enhancing drug permeability.^{138,139} For example, one design features pH/reactive oxygen species (ROS) cascade-responsive prodrug micelles. In the acidic TME, these micelles undergo a charge reversal, releasing siRNA targeting transforming growth factor-beta (siTGF- β). This silences TGF- β in CAFs, inhibiting their activity, remodeling the immunosuppressive TME, and thereby enhancing drug permeability.¹⁴⁰ Subsequently, in response to high intratumoral ROS levels, the micelles shrink in size, releasing encapsulated chemotherapeutic agents like doxorubicin to directly kill tumor cells.¹⁴¹ This CAF inhibition and consequent TME normalization improve the delivery efficiency of chemotherapeutics, creating a synergistic treatment effect. Multi-stimulus-responsive nanosystems can enable precise spatiotemporal control of drug delivery. For example, nanomaterials that respond to external stimuli such as heat or light can be used to remotely trigger the release of immunomodulatory agents. One approach is a sequential release strategy in which an initial external trigger, such as near-infrared irradiation, releases CAF inhibitors to modulate the tumor microenvironment, followed by endogenous cues including specific enzymes or reactive oxygen species that drive the release of chemotherapeutic or immunotherapeutic agents to promote systemic antitumor immunity.¹⁴² For PCa, PSMA-targeted NPs have been designed to co-deliver the chemotherapeutic docetaxel and PD-L1 siRNA. This system enhances targeting and therapeutic efficacy by simultaneously attacking cancer cells and reversing the immunosuppressive TME. To further address CAF-mediated immunosuppression, Chen et al developed RGD peptide-modified lipid nanoparticles (RGD-LNPs). These nanoparticles were designed to deliver TGF- β siRNA to $\alpha\beta3$ integrin-enriched stromal cells, including CAFs. In preclinical models, silencing TGF- β in CAFs was associated with reduced ECM deposition and a decrease in the secretion of immunosuppressive factors such as IL-10 and VEGF. These stromal changes were accompanied by increased T cell infiltration and a shift toward a more inflamed immune contexture, suggesting a potential attenuation of “immune-cold” features.¹⁴³ Furthermore, in a mouse pancreatic cancer model, combining this CAF-targeted TGF- β silencing approach with an anti-PD-L1 antibody significantly inhibited tumor growth and metastasis, with enhanced antitumor activity compared with either monotherapy, including reports of complete responses in a subset of animals (up to 60% in that study). Notably, these findings remain preclinical and may depend on tumor type and

model context. Another strategy involves loading RGD-LNPs with a Stimulator of Interferon Genes (STING) agonist, such as cyclic GMP-AMP (cGAMP), to promote innate immune activation within the tumor microenvironment. This approach can activate a type I interferon response in TAMs. When combined with CD47 blockade (“don’t eat me” signal inhibition), it has been reported to synergistically promote tumor cell phagocytosis by macrophages and may induce abscopal antitumor immune responses.¹⁴⁴ Collectively, these combinatorial nanomedicine strategies show promising antitumor efficacy in preclinical settings and support the concept that CAF- and myeloid-directed immunomodulation can potentially improve responses to immune checkpoint blockade, although further validation in additional models and clinical studies is needed.

CAF-Targeted Nanotheranostics and Imaging

Theranostics, which integrates diagnostic imaging with therapy, is gaining prominence in precision medicine for PCa. By targeting CAFs within the tumor microenvironment, this approach can enable real-time monitoring of treatment response and facilitate iterative optimization of therapeutic regimens.⁹⁵ CAFs, which often exhibit high expression of markers such as FAP, represent a key target for rational nanomaterial design. Such nanomaterials can be co-loaded with imaging agents, including magnetic nanoparticles or fluorescent probes, and therapeutic cargos, such as chemotherapeutics or small interfering RNA, thereby enabling concurrent tumor visualization and therapeutic intervention in PCa.^{54,62} Recent studies demonstrate that CAF-targeted liposomal or polymeric nanocarriers can enhance MRI contrast, inhibit metastasis by remodeling the TME, and improve overall therapeutic efficacy when combined with immunotherapy.^{53,145} This section systematically reviews the biological rationale, design principles, and clinical translation potential of CAF-targeted nanotheranostics. It aims to provide a theoretical foundation for integrated diagnostic and therapeutic strategies in PCa (Figure 6).

CAF-Targeted Imaging Probes

In certain cancers, such as breast, pancreatic, and colorectal carcinomas, CAFs and associated fibrous tissue can constitute over 90% of the tumor mass. The specific expression of FAP on CAFs makes it an ideal target for theranostic applications. This is exemplified by targeted probes like ⁶⁸Ga-FAPI, which have demonstrated significant clinical potential.¹⁴⁷ However, the pronounced heterogeneity of CAFs in PCa demands imaging probes with higher specificity. This challenge is driving the development of advanced, multifunctional probes. Consequently, the field of CAF-targeted imaging has evolved from single-modality probes towards multifunctional integrated platforms, creating new pathways for precise PCa theranostics. This evolution has been propelled by foundational research, such as that from the Foster team.¹⁴⁸ Through cross-species multi-omics analysis, they identified three conserved CAF subtypes: homeostatic, mechanoreactive, and immunomodulatory. This discovery provides a crucial theoretical framework and highlights the potential for developing broad-spectrum imaging probes capable of distinguishing between CAF subtypes. Building on this, preclinical work by Li et al has shown that ⁶⁸Ga-FAPI PET imaging enables not only high-sensitivity detection of tumor lesions but also real-time monitoring of CAF dynamics following therapy targeting the TGF- β pathway in combination with immunotherapy. This provides a crucial strategy for monitoring and overcoming the immunosuppressive microenvironment and therapy resistance in PCa bone metastases.¹⁴⁷ Parallel innovations in probe technology are also underway. For instance, Jiang et al developed a ^{99m}Tc-labeled HYNIC-FAPI probe with favorable radiochemical properties and low hepatic background.¹⁴⁹ This makes it a cost-effective candidate for SPECT imaging, particularly useful for complementing PSMA imaging to reveal tumor heterogeneity stemming from both epithelial and stromal compartments. Furthermore, the carrier systems for probes are converging with nanotechnology. Santos-Coquilla et al pioneered a dual-labeled platform based on small extracellular vesicles, which naturally encapsulate both radioactive and fluorescent labels.¹⁵⁰ These vesicles are actively taken up by CAFs in the TME, paving the way for future CAF-targeted nanomedicines that combine diagnostic imaging and drug delivery. This approach holds promise for ultimately achieving precise visualization and therapeutic intervention of key CAF subpopulations that drive therapy resistance in CRPC.

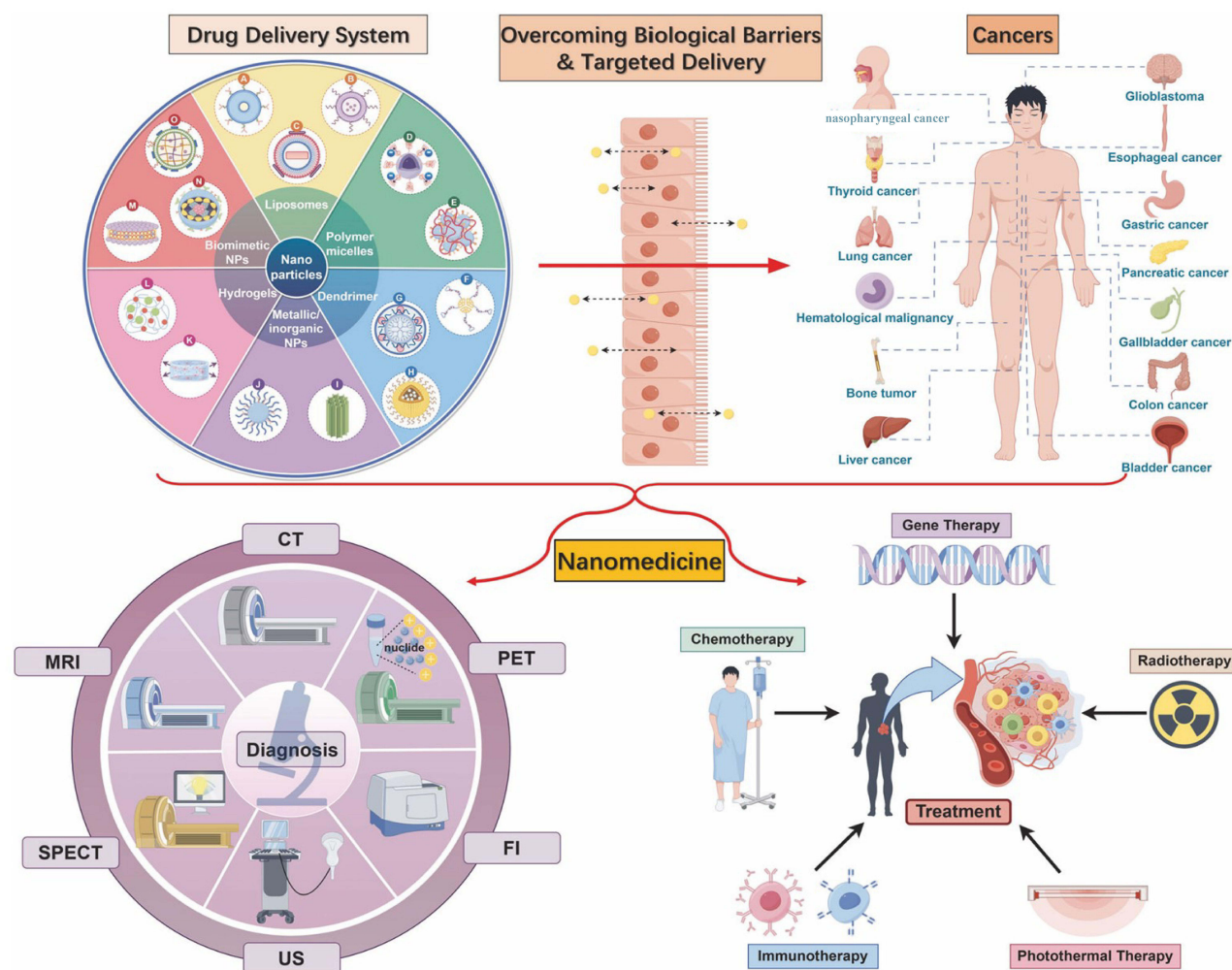


Figure 6 Nanomedicine-enabled integration of cancer diagnosis and treatment. This schematic illustrates how nanoparticle-based drug delivery systems can facilitate targeted delivery across biological barriers and support combined diagnostic and therapeutic applications. The upper panel summarizes representative nanocarrier platforms (e.g., liposomes, polymer micelles, dendrimers, metallic/inorganic nanoparticles, hydrogels, and biomimetic nanoparticles) and depicts their transport across physiological barriers toward tumors in different anatomical sites. The lower-left panel highlights common imaging modalities used for nanotheranostics, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), fluorescence imaging (FI), and ultrasound (US). The lower-right panel summarizes major treatment modalities that can be delivered or enhanced by nanomedicine, including chemotherapy, gene therapy, immunotherapy, radiotherapy, and photothermal therapy. Symbols and graphical elements: Solid arrows indicate the direction of nanoparticle transport and the conceptual linkage between nanomedicine platforms and downstream diagnostic or therapeutic outputs. Dotted connector lines from the human body to specific organs indicate representative tumor sites across cancer types. Reproduced from,¹⁴⁶ Copyright © 2024 by authors.

Abbreviations: NP, nanoparticle; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; FI, fluorescence imaging; US, ultrasound.

Visualized Drug Release Systems

The development of visualized drug release systems targeting CAFs in PCa relies on integrating three key elements: specific target discovery, multifunctional nanomaterials, and theranostic strategies. Pioneering research by Ataeinia et al demonstrated the feasibility of visualizing and targeting PCa CAFs.¹⁵¹ Their study identified lysosome-associated membrane protein 1 (LAMP1) as a key surface marker on CAFs and developed a zirconium-89-labeled anti-LAMP1 antibody (⁸⁹Zr-DFO-anti-LAMP1). This probe enabled the first non-invasive, in vivo visualization of CAFs via PET/CT, providing crucial validation for CAF-targeted strategies. Furthermore, Pranva et al noted that nanocarriers can be co-loaded with diverse imaging agents beyond PET tracers, such as MRI contrast agents (e.g., gadolinium chelates), fluorescent dyes, and near-infrared probes. This multimodal imaging capability allows for the real-time, non-invasive monitoring of CAF distribution, density, and associated nanomedicine accumulation in vivo.¹⁵² Building on this, a review by Fang et al highlights an advanced theranostic approach: constructing intelligent nanoplateforms that integrate CAF-

targeting ligands (e.g., against LAMP1 or FAP) with multimodal imaging probes (for PET, MRI) to achieve simultaneous precise imaging and controlled drug release in PCa.¹⁵³ These developments collectively support a comprehensive precision medicine workflow. It begins with patient stratification using whole-body PET and targeted molecular probes to identify individuals with CAF-rich tumors. Following this, CAF-targeted nanomedicines are administered to achieve localized accumulation. The cycle concludes with longitudinal molecular imaging to monitor changes in CAF distribution and activity before and after treatment, enabling real-time assessment of therapeutic response and facilitating end-to-end management of PCa therapy.

Translation and Challenge

As detailed in this review, CAFs engage in intricate crosstalk within the PCa TME. They play critical roles in disease progression, metastasis, and therapy resistance. CAFs have heterogeneous origins. These include tissue-resident fibroblasts, mesenchymal stem cells, and perivascular or adipose-derived precursors. This cellular diversity gives rise to functionally distinct subtypes (e.g., myCAF, iCAF, apCAF) that orchestrate ECM remodeling, immune suppression, and metabolic reprogramming via key pathways like TGF- β /SMAD, IL-6/STAT3, and CXCL12/CXCR4.⁵³ This functional plasticity amplifies tumor invasiveness and chemoresistance. Furthermore, CAFs act as protective barriers in the TME, limiting drug penetration and promoting immune evasion, thereby posing significant challenges to traditional therapies.¹⁵⁴ Advances in single-cell RNA sequencing and proteomic analyses have helped identify CAF-associated markers such as FAP, α -smooth muscle actin, and LOXL2, enabling more refined subtyping and associating specific CAF states with adverse outcomes in high-grade PCa. However, CAFs dynamically interact with other components of the tumor microenvironment, including tumor cells undergoing epithelial–mesenchymal transition, immunosuppressive populations such as regulatory T cells and myeloid-derived suppressor cells, and pro-angiogenic vascular elements. Together, these interactions highlight the need for multifaceted therapeutic strategies that concurrently address stromal remodeling, immune suppression, and tumor cell plasticity.¹⁵⁵

Nanomedicine has emerged as a versatile platform to address these complexities by enabling targeted delivery, controlled release, and theranostic applications that modulate CAFs. Both organic nanocarriers, such as liposomes and polymeric nanoparticles, and inorganic nanomaterials, such as gold nanoparticles and mesoporous silica, can be functionalized with targeting ligands including anti-FAP single-chain variable fragments, RGD peptides, or enzyme-responsive moieties. Such functionalization can enhance tumor accumulation through the enhanced permeability and retention effect and ligand-mediated uptake, and may reduce off-target toxicity.⁶ Promising preclinical strategies include: CAF ablation using navitoclax-loaded liposomes; CAF reprogramming via pH-responsive micelles carrying TGF- β inhibitors; and ECM degradation using collagenase-encapsulated NPs. These approaches reduce matrix density, improve drug penetration, and can synergize with immunotherapy to convert immunologically “cold” tumors into “hot” ones. For instance, multimodal NPs combining PTT with CAF-targeted siRNA delivery have been shown to disrupt the THBS2-SDC4-EMT axis and inhibit metastasis in PCa models.^{6,120} Furthermore, CAF-guided theranostics, exemplified by tracers like ⁶⁸Ga-FAPI for PET, enable real-time imaging of stromal activation. This capability can guide personalized intervention strategies and monitor treatment responses. These innovations align with recent advances. For example, a strategy employing ultrasound-mediated infiltration and ROS-induced iron death (ferroptosis) has shown excellent efficacy against drug-resistant PCa subtypes.¹⁴⁶

Despite these advances, significant limitations hinder the clinical translation of CAF-targeted nanomedicines. CAF heterogeneity, influenced by tumor stage and prior therapy, can drive adaptive resistance. Depleted CAF subpopulations may be replenished from alternative precursor pools, potentially exacerbating disease progression in some contexts.¹⁵⁵ Key challenges for nanomaterials include unpredictable biodistribution, which can arise when tumor microenvironment acidity alters nanoparticle surface charge; rapid immune clearance of designs lacking biomimetic features; and scalability constraints for good manufacturing practice compliant production.¹⁵⁶ Clinical trials evaluating CAF-targeted nanomedicines in PCa, including formulations combining FAP inhibitors with nanoparticles, remain limited. Most supporting evidence is derived from preclinical models, which do not fully recapitulate the complexity and heterogeneity of the human tumor microenvironment.^{157,158} Moreover, CAFs can exert context-dependent functions, promoting tumor progression in advanced disease while potentially restraining tumor growth at earlier stages. This duality underscores

the need for subtype-informed targeting strategies to minimize unintended protumorigenic effects. Integrating multi-omics datasets with artificial intelligence driven predictive modeling may help optimize target selection, payload design, and patient stratification. However, potential nanotoxicity, long-term biodistribution, and biosafety considerations should be prioritized throughout preclinical development and clinical translation. In summary, CAF-targeted nanomedicine integrates stromal biology with nanotechnology and offers a framework to disrupt tumor-supportive microenvironmental programs in PCa. Addressing current gaps will require cross-disciplinary collaboration across oncology, immunology, and biomaterials science, which will be essential for translating CAF-directed nanomedicines into clinically meaningful improvements in patient outcomes.

Future Perspectives

The clinical translation of CAF-targeted nanomedicine for PCa will benefit from focused exploration of several promising avenues. First, genome-editing strategies delivered via hybrid NPs could advance subtype-specific therapy. For example, Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-Associated Protein 9 (CRISPR-Cas9) systems could be used to precisely reprogram pro-tumorigenic iCAFs into an anti-tumor state while sparing potentially beneficial CAF subtypes. Although such approaches remain largely preclinical, advances in transient and tissue-restricted gene-editing delivery platforms may improve safety and feasibility in future translational applications.⁶ Second, advanced nanocarrier designs that incorporate emerging technologies may enable improved spatiotemporal control of drug release. Examples include DNA origami nanostructures and engineered extracellular vesicles designed for multi-stimuli-responsive release in response to pH changes, reactive oxygen species, or tumor-associated enzymes. Third, combination strategies may further enhance therapeutic efficacy. Combining CAF-targeted nanomedicines with established treatments, including androgen receptor targeted therapy such as enzalutamide and PSMA-targeted radioligand therapy such as ¹⁷⁷Lu-PSMA, may improve outcomes in metastatic castration-resistant prostate cancer. The broader rationale for multimodal intensification is supported by clinical evidence. For example, in the PCS IX trial, adding stereotactic body radiotherapy improved radiographic progression-free survival. Translational efforts should prioritize early-phase clinical trials to establish safety, pharmacokinetics, and biodistribution. Such trials could evaluate CAF-targeted nanoparticles in biomarker-stratified cohorts and incorporate molecular imaging, such as FAPI-PET, to support patient selection and on-treatment monitoring of stromal engagement.¹⁵⁹ Fourth, artificial intelligence driven design and optimization may accelerate innovation in CAF-targeted nanomedicine. Machine learning algorithms can be used to model and optimize key nanoparticle parameters, including particle size, surface properties, and ligand density, which may streamline the development of next-generation CAF-targeted nanomedicines. Fifth, targeting CAF metabolism and modulating senescence may represent a complementary therapeutic strategy. Nanoformulations delivering pro-oxidant agents, such as naphthoquinones, have been reported to promote senescence-like phenotypes in CAFs by exploiting metabolic vulnerabilities. In preclinical models, these approaches can disrupt recycling pathways including autophagy. Careful evaluation will be required to balance antitumor benefit against the potential accumulation of senescent stromal cells and associated inflammatory effects. Finally, the rapid clinical development of mRNA-based cancer vaccines and their reliance on lipid nanoparticle (LNP) delivery platforms, future research should explore the integration of PCa-directed mRNA vaccines with CAF modulation strategies.¹⁶⁰ mRNA vaccines encoding tumor-associated antigens (e.g., PSMA, PAP, or neoantigens identified through tumor sequencing) have demonstrated immunogenicity in early-phase studies.^{161,162} However, the immunosuppressive stromal milieu in advanced PCa may limit durable T cell priming and infiltration. In this context, CAF-targeted nanomedicine approaches that attenuate TGF- β signaling, reduce ECM barriers, or normalize stromal architecture could theoretically enhance mRNA vaccine-induced antitumor immunity.¹⁶³ Although direct clinical evidence for such synergy in PCa is currently limited, the shared reliance on lipid nanoparticle technologies and immune activation pathways provides a compelling translational rationale for combined investigation.¹⁶⁴ Addressing translational barriers and equitable access is a critical priority. This will require the development of biodegradable nanomaterials to reduce concerns regarding long-term toxicity, as well as scalable and cost-effective platforms that support broad global accessibility. Continued development of CAF-directed theranostic platforms is also important. Nanoplatforms that integrate diagnostic capabilities, such as FAP-targeted imaging probes, can enable real-time assessment of CAF heterogeneity and treatment response, thereby supporting iterative adjustment of therapeutic

strategies. Furthermore, elucidating CAF and cancer stem cell crosstalk and integrating this knowledge into nano-enabled combination therapies, such as photothermal therapy or photodynamic therapy, may reveal new approaches to limit metastasis, a major driver of prostate cancer mortality.

In conclusion, pursuing these interconnected research avenues is expected to accelerate the clinical translation of CAF-targeted nanomedicine, paving the way for more personalized and effective treatment strategies that ultimately improve patient outcomes in PCa. Current breakthroughs in immunotherapy-enhanced nano-strategies provide a strong foundation for these efforts, positioning the precise regulation of CAFs as a cornerstone for next-generation PCa therapies.³²

Conclusion

In conclusion, this review synthesizes the critical role of CAFs in PCa progression, emphasizing their biological foundations, heterogeneous subtypes, and interactions within the TME. By targeting key molecules such as FAP and TGF- β pathways, nanotechnology—through diverse nanomaterials, targeted modifications, and strategies like CAF ablation, reprogramming, and ECM degradation—offers innovative solutions to overcome therapeutic resistance and enhance drug delivery. CAF-directed theranostics further enable precise imaging and treatment integration, paving the way for personalized medicine. Despite challenges in CAF heterogeneity and nanomaterial safety, these advancements promise improved outcomes in castration-resistant PCa. Future translational research will be essential to fully realize this potential in clinical precision oncology.

Abbreviation

PCa, Prostate Cancer; CAFs, Cancer-Associated Fibroblasts; TME, Tumor Microenvironment; α -SMA, Alpha-Smooth Muscle Actin; FAP, Fibroblast Activation Protein; myCAF, Myofibroblastic Cancer-Associated Fibroblasts; iCAF, Inflammatory Cancer-Associated Fibroblasts; apCAF, Antigen-Presenting Cancer-Associated Fibroblasts; ECM, Extracellular Matrix; PDGFR β , Platelet-Derived Growth Factor Receptor Beta; TGF- β , Transforming Growth Factor Beta; EMT, Epithelial-Mesenchymal Transition; AR, Androgen Receptor; CRPC, Castration-Resistant Prostate Cancer; ADT, Androgen Deprivation Therapy; PSMA, Prostate-Specific Membrane Antigen; EPR, Enhanced Permeability and Retention Effect; NPs, Nanoparticles; scRNA-seq, Single-Cell RNA Sequencing; IHC, Immunohistochemistry; ELISA, Enzyme-Linked Immunosorbent Assay; qRT-PCR, Quantitative Reverse Transcription Polymerase Chain Reaction; MSCs, Mesenchymal Stem Cells; (BM-MSCs, Bone Marrow-Derived Mesenchymal Stem Cells; ASCs, Adipose-Derived Stem Cells; PPAT, Periprostatic Adipose Tissue; EndMT, Endothelial-to-Mesenchymal Transition; FSP-1, Fibroblast-Specific Protein-1; CXCL12, C-X-C Motif Chemokine Ligand 12; CXCR4, C-X-C Motif Chemokine Receptor 4; VEGF, Vascular Endothelial Growth Factor; MDSCs, Myeloid-Derived Suppressor Cells; M-MDSCs, Monocytic Myeloid-derived Suppressor Cells; TAMs, Tumor-Associated Macrophages; LOX, Lysyl Oxidase; MMP, Matrix Metalloproteinase; HA, Hyaluronic Acid; CHA NPs, Chitosan-hyaluronic Acid Nanoparticles; FN1, Fibronectin 1; TNC, Tenascin-C; SPIONs, Superparamagnetic Iron Oxide Nanoparticles; PEG, Polyethylene Glycol; siRNA, Small Interfering RNA; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging; SPECT, Single Photon Emission Computed Tomography; CT, Computed Tomography; FI, Fluorescence Imaging; US, Ultrasound; AI, Artificial Intelligence; GMP, Good Manufacturing Practice; ROS, Reactive Oxygen Species; GSH, Glutathione; LIFU, Low-Intensity Focused Ultrasound; PTT, Photothermal Therapy; PDT, Photodynamic Therapy; STING, Stimulator of Interferon Genes; cGAMP, Cyclic GMP-AMP; ADC, Antibody-Drug Conjugate; CAR-T, Chimeric Antigen Receptor T-Cell; scFv, Single-Chain Variable Fragment; RGD, Arginine-Glycine-Aspartic Acid; LAMP1, Lysosome-Associated Membrane Protein 1; CRISPR-Cas9, Clustered Regularly Interspaced Short Palindromic Repeats – CRISPR-Associated Protein 9; SBRT, Stereotactic Body Radiotherapy; rPFS, Radiographic Progression-Free Survival; CSC, Cancer Stem Cell; MSNs, Mesoporous Silica Nanoparticles; Tregs, Regulatory T Cells; ICI, Immune-checkpoint Inhibitor; PD-1/PD-L1, Programmed Cell Death Protein 1/Ligand 1; MHC, major histocompatibility complex; CTL, Cytotoxic T Lymphocyte; DC, Dendritic cell; TAN, Tumor-Associated Neutrophil; CTLA4, Cytotoxic T-Lymphocyte-Associated Protein 4; LAG3, Lymphocyte-activation Gene 3; TIM3, T-Cell Immunoglobulin And Mucin Domain 3; PLGA, Poly (Lactic-Co-Glycolic Acid); PDA, Polydopamine; BSA, Bovine Serum Albumin; CD, Carbon Dot; BP, Black Phosphorus; MOF, Metal–Organic Framework; NK cell, Natural Killer cell; EV, Extracellular Vesicle.

Availability of data and materials

No new data has been generated, all references are cited in the manuscript.

Consent for publication

All the authors were consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no competing interests associated with the manuscript.

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