Cancer Nanotechnology

RESEARCH Open Access

Nanomaterials in cancer immunotherapy: targeting cancer-associated fibroblasts

Zhongsong Zhang[1,2] and Long Chen[1,2*]

*Correspondence:
chenlong@cmc.edu.cn

[1] School of Clinical Medicine, Chengdu Medical College, Chengdu, China
[2] School of Basic Medical Sciences, Chengdu Medical College, Chengdu, China

Abstract

Emphasizing the significance of cancer-associated fibroblasts (CAFs), non-malignant yet pivotal players within the tumor microenvironment (TME), this review illuminates the role of inflammatory subtype (iCAF) as catalysts in cancer proliferation, metastasis, and therapeutic resistance. Given their paramount importance, targeting CAFs emerges as a robust strategy in the evolving landscape of cancer immunotherapy. Nanomaterials, distinguished by their unique features and malleability, hold considerable promise in biomedicine, especially in the precision-oriented domain of cancer therapy. Their aptitude for modulating immune responses, amplifying drug efficacy through precise delivery, and discerningly focusing on cells within the TME situates nanomaterials as formidable tools to transcend the boundaries set by conventional treatments. This review scrutinizes the convoluted interplay among CAFs, immune cells, and tumor cells within the TME. It further showcases widely utilized nanomaterials in cancer management. We underscore the potential of nanoscale drug delivery systems directed at CAFs, underscoring their transformative power in revolutionizing cancer therapies, enhancing precision, and culminating in improved patient outcomes.

Keywords: Cancer-associated fibroblasts, Drug delivery, Nanomedicine, Tumor microenvironment, Cancer immunotherapy

Introduction

Cancer remains one of the most formidable health challenges worldwide (Li et al. 2024a), with TME playing a critical role in cancer progression and resistance to therapy (Xiang et al. 2022; Hu et al. 2020a). Among the various components of the TME, CAFs have emerged as key players in facilitating tumor growth and metastasis. CAFs contribute to numerous aspects of tumor biology, including promoting tumor growth and metastasis, enhancing drug resistance, remodeling the TME, and inducing immunosuppression (Burley et al. 2022). For instance, CAFs have been shown to transfer exosomes to colorectal cancer cells (CRC), significantly increasing the levels of miR-92a-3p, which leads to metastasis and chemotherapy resistance in CRC patients (Hu et al. 2019). These cells not only support the structural integrity of tumors through extracellular matrix (ECM) deposition, but also modulate immune responses, thus contributing to a complex network of interactions that promote tumor survival and resistance to treatments (Lu et al. 2023; Piersma et al. 2020).

Furthermore, the existence of different subtypes and phenotypes of CAFs across different tumors complicates the development of universal targeting strategies. In recent years, the heterogeneity of CAFs has emerged as a pivotal factor in cancer progression and therapy resistance (Montazersaheb et al. 2024). These cells, once considered uniform, are now understood to exhibit diverse subtypes—each with distinct molecular signatures and roles within the TME. This complexity underscores the necessity of developing targeted therapies that address specific CAF functions to effectively combat cancer (Chen et al. 2021). Given their pivotal role, CAFs represent a promising target for therapeutic intervention in cancer immunotherapy.

Recent advances in nanotechnology have opened new avenues for cancer treatment, particularly through the development of nanomaterials that can be precisely engineered to target specific cellular functions within the TME (Liu et al. 2023a; Liang et al. 2024a; Gu et al. 2024). Nanomaterials offer unique properties, such as small size, large surface area to mass ratio, and the ability to encapsulate or conjugate with various therapeutic agents, making them ideal candidates for overcoming some of the limitations associated with conventional cancer therapies (Rosic 2024; Li et al. 2024b). Different types of nanomaterials, including organic and inorganic varieties, offer distinct physicochemical properties that provide significant advantages in drug delivery and treatment (Liu et al. 2022a; Hu et al. 2024a; Kimiz-Gebologlu and Oncel 2022; Huseynov 2024). These materials can be engineered to target CAFs specifically, modifying the TME to enhance anti-tumor immunity (Gong et al. 2019; Wu et al. 2024). Targeting CAFs with nanomaterials disrupts the fibrotic stroma, reduces ECM deposition, and alleviates the immunosuppressive environment (Cheng et al. 2024a). This disruption not only enhances the infiltration of immune cells and therapeutic agents into the tumor core but also facilitates improved treatment efficacy (Zhu et al. 2022). Additionally, nanomaterials can be designed to carry immunomodulatory agents, promoting the activation and proliferation of immune cells within the TME (Tong et al. 2022). For example, nanoparticles targeting CAFs can dismantle the immunosuppressive stroma, allowing for increased infiltration and activity of cytotoxic T lymphocytes, thereby boosting immune responses against the tumor (Han et al. 2022). Specifically, the targeting of CAFs with nanomaterials presents an innovative approach to modulate the tumor stroma, potentially enhancing the efficacy of immunotherapeutic agents (Wu et al. 2024; Jian et al. 2024).

Nanomedicine, as a leading-edge approach in cancer therapy, offers targeted delivery systems that reduce systemic toxicity and improve therapeutic outcomes (Montazersaheb et al. 2024; Huseynov 2024; Liu et al. 2019a). In conclusion, nanomedicine targeting CAFs holds significant promise for advancing cancer immunotherapy (Wang et al. 2023a). By leveraging the unique properties of nanomaterials, these systems can precisely regulate the TME, thereby enhancing both local and systemic immune responses (Hong et al. 2025; Liu et al. 2024a). This approach has the potential to improve treatment outcomes, survival rates, and the quality of life for cancer patients.

Method

We conducted a comprehensive search of the PubMed database for English-language publications from 2019 to 2024, using the keywords 'cancer-associated fibroblasts (CAFs)', 'nanomedicine', 'drug delivery', 'tumor microenvironment (TME)', and 'cancer immunology'. This search yielded a total of 921 articles. Following a thorough

screening process, studies lacking relevance to CAFs, nanomedicine, and TME interactions were excluded. Based on predefined inclusion criteria, 394 articles were selected for detailed analysis, focusing on recent advancements in CAF-targeting strategies, the role of nanomaterials in drug delivery, and their interactions within the TME and cancer immunotherapy.

What is CAF?

CAF subtypes: origins, functions, and their role in cancer therapy

CAFs arise from various cellular origins, with one common source being normal fibroblasts recruited by tumor cells, which are subsequently converted into CAFs (Rimal et al. 2022). Additionally, CAFs can emerge from the transformation of other cell types, such as endothelial and epithelial cells, mesenchymal stem cells, and adipocytes, as well as from the differentiation of tumor stem cells (Kobayashi et al. 2022; Zhang et al. 2023a; Tang et al. 2022). The origin of CAFs may also be influenced by physiological conditions, tumor type, environmental factors, and other variables (Sahai et al. 2020; Santi et al. 2018). For example, studies have shown that in breast cancer, adipocytes can undergo dedifferentiation into CAFs (Jotzu et al. 2010). Interestingly, a lack of certain substances in specific environments can also induce CAF differentiation (Ferrer-Mayorga et al. 2017). For instance, Jerome Thiery's research highlights that deficiencies in vitamins A or D can promote CAF differentiation in some cases (Thiery 2022). However, further research is needed to fully explore the various origins of CAFs under different conditions.

Moreover, different subtypes of CAFs exhibit distinct biological characteristics and functions (Huang et al. 2023; Cortez et al. 2014), such as invasive CAFs, immunosuppressive CAFs, stromal CAFs, and degenerative CAFs. Invasive CAFs contribute to tumor invasion and metastasis (Yin et al. 2024), immunosuppressive CAFs help tumors evade immune surveillance (Pradip et al. 2021), stromal CAFs play a key role in constructing the tumor microenvironment (Dong et al. 2024), and degenerative CAFs are primarily associated with tumor drug resistance (Zhu et al. 2018). Generally, CAFs are often categorized into three major groups: myofibroblasts (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) (Wang et al. 2024a; Maia and Wiemann 2021; Foster et al. 2022). Myofibroblastic CAFs (myCAFs) are characterized by the expression of alpha-smooth muscle actin (α-SMA) and are primarily involved in matrix deposition and remodeling (Li et al. 2024c; Geng et al. 2021). Inflammatory CAFs (iCAFs) secrete cytokines and chemokines that modulate immune responses, marked by the expression of S100A4 (Friedman et al. 2020; Santolla et al. 2021). Antigen-presenting CAFs (apCAFs) have recently been identified for their capability to present antigens and interact with T cells (No Author 2022; Huang et al. 2022a; Kerdidani et al. 2022), although their markers are still being explored (Yamashita and Kumamoto 2024; Guo and Xu 2024). iCAFs contribute to creating an immunosuppressive environment that supports tumor growth by secreting inflammatory mediators (Guo and Xu 2024; Monteran and Erez 2019), while myCAFs enhance tumor stiffness and fibrosis, affecting drug penetration and efficacy (Bates et al. 2023). apCAFs represent a potential target for immunotherapy due to their role in modulating T-cell activity within the TME (Kerdidani et al. 2022). Understanding these CAF subtypes and their unique role in

TME allows us to design more effective nanomaterial-based therapies (Rosic 2024; Singh et al. 2024a; Wang et al. 2024b; Peng et al. 2024), for example, we can develop nanoparticles that simultaneously target multiple CAF subtypes or combine CAF targeting with direct anticancer effects (Huang et al. 2024a). Specifically, a new nanoparticle could be designed to carry both TGF-β inhibitors (for myCAFs) and siRNA, a cytokine for iCAFs (D'Aversa et al. 2024; Yang et al. 2023a; Wu et al. 2023). We can even tailor the nanoparticle treatment regimen to the patient based on the CAF population that dominates the patient's tumor, thus achieving personalized treatment (Tian et al. 2024; Su et al. 2023).

Interestingly, some studies suggest that balancing the number of CAF subgroups may offer important clinical benefits (Foster et al. 2022). This indicates the potential for patient-specific treatments based on the number and type of CAF subpopulations (Hu et al. 2021). Different CAF subtypes exist in various tissues and organs, and understanding their unique characteristics and functions is essential for developing new strategies for targeted therapies (Helms et al. 2022). The presence of multiple CAF subtypes within different tumors and tissues suggests that these cells may play diverse roles in various diseases (Houthuijzen et al. 2023; Sung and Lee 2024). Gaining deeper insights into the functions of CAF subtypes will contribute to our understanding of the tumor microenvironment and its regulatory mechanisms, offering potential new directions for targeted cancer therapy (Fig. 1) Yang et al. 2023b.

CAF markers: key players in tumor progression and therapy

CAFs and their associated markers play a crucial role in tumor progression, particularly through their varied biological functions in the TME (Pan et al. 2024). Understanding these markers is essential for advancing our comprehension of cancer immunotherapy. Currently, it is widely accepted that CAF markers hold significant clinical relevance (Simon and Salhia 2022). For example, these markers are valuable tools for identifying and tracking the development of tumors (Gadd et al. 2022). Clinicians can use these markers to diagnose tumors and assess disease severity by detecting them in blood or tissue samples (Li et al. 2018a). Additionally, CAF markers can help predict a tumor's response to different treatments and monitor the effectiveness of therapies. Given this, the clinical potential of CAF markers is promising (Zhang et al. 2023b).

The discovery of CAF markers has been a challenging and ongoing process. α-Smooth muscle actin (α-SMA), first identified in the 1970s by Gabbiani and colleagues in studies on wound healing, remains one of the most widely recognized markers of CAFs and is commonly used for their identification (Tarbit et al. 2019; Muchlińska et al. 2022). However, recent research indicates that α-SMA-positive CAFs may exhibit both pro-tumorigenic and anti-tumorigenic properties (Shinde et al. 2017; Elewa et al. 2024). Another classic marker is fibroblast activation protein (FAP), a membrane protein discovered in the early 1990s in interstitial cells and certain cancers (Fitzgerald 2024). Platelet-derived growth factor receptor (PDGFR), highly expressed in CAFs and linked to their activation and tumor-promoting roles, was identified by Jan-Åke Gustafsson and Charles-Henri Heldin during molecular cloning experiments in 1978 (Matsui et al. 1989).

With advancements in detection techniques, scientists have identified an array of CAF markers using methods like single-cell sequencing (Lavie et al. 2022). Additional markers include Vimentin, fibronectin (FN), laminin (LN), matrix metalloproteinases

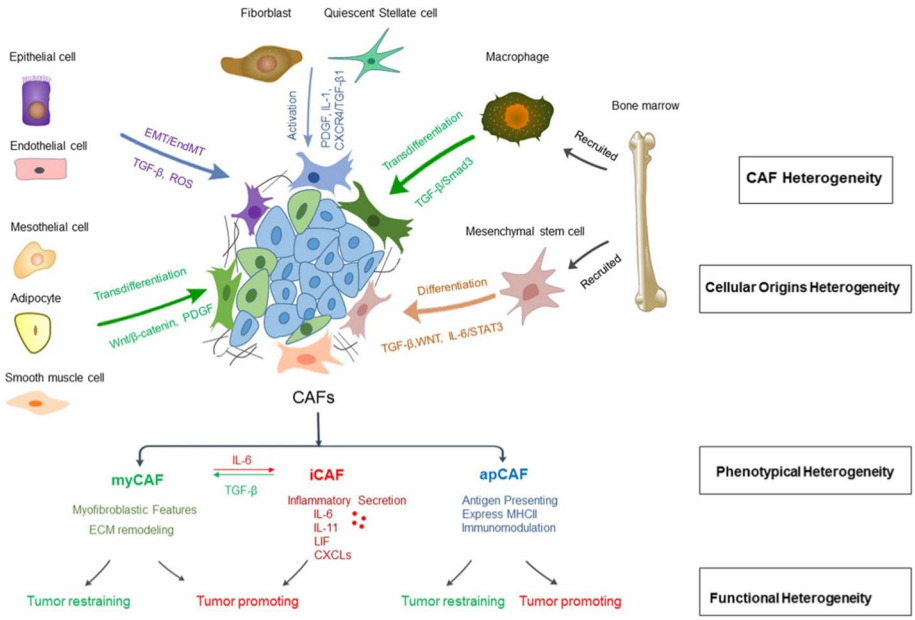

Fig. 1 CAF subtypes: origins, functions, and their role in cancer therapy. The illustration depicts the diverse cellular origins, heterogeneity, and functional roles of CAFs within the tumor microenvironment. CAFs can originate from various cell types, including epithelial cells, endothelial cells, mesothelial cells, adipocytes, smooth muscle cells, or differentiate from bone marrow-derived mesenchymal stem cells. The figure also highlights three major CAF subtypes: myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs), which are involved in extracellular matrix remodeling, cytokine secretion, and immune modulation, respectively. These CAF subtypes display distinct functions, either promoting or restraining tumor progression, reflecting the phenotypic and functional heterogeneity of CAFs. Reproduced fromYang et al. 2023b, Copyright © 2023 by the authors

(MMPs), epithelial cell adhesion molecule (EPCAM), synovial glycoprotein (SGR), and mannose-binding lectin (MBL) (Hernández-Jiménez et al. 2022; Nurmik et al. 2020; Mao et al. 2021; Zhao et al. 2023). Interestingly, in breast cancer-associated fibroblasts, specific genes such as NOTCH3 and HES4 have been found to serve as markers involved in CAF self-renewal and proliferation (Bartoschek et al. 2018). This discovery suggests a potential new method of integrating gene technology with these specific markers, offering a novel direction for future research.

While many new markers have been identified, the number of known fibroblast biomarkers remains limited (Xia et al. 2024). A key challenge moving forward is distinguishing between normal fibroblasts, CAFs, and different CAF subtypes using simple markers (Nurmik et al. 2020). This distinction is crucial for understanding CAF heterogeneity and improving targeted therapies. Hopefully, further research will provide answers to these challenges in the near future.

The multifaceted role of cancer-associated fibroblasts in tumor progression and treatment implications

The relationship between CAFs, tumors, and tumor cells is complex and has significant implications for patient prognosis (Koumpis et al. 2024; Wang et al. 2024c). Studies suggest that the quantity and activity of CAFs are closely correlated with the prognosis of cancer patients (Qin et al. 2023). However, the impact of CAFs on tumor development

and prognosis is multifaceted, influenced by various factors (Caramelo et al. 2023). During cancer progression, CAFs interact with tumor cells by expressing extracellular signaling molecules such as osteopontin (OPN) and hepatocyte growth factor (HGF), which influence tumor cell proliferation, invasion, and migration (Ping et al. 2021). These interactions demonstrate how CAFs can significantly shape the TME.

In the TME, CAFs regulate tumor growth through several mechanisms, including metabolic modulation. They affect processes such as glucose regulation and pH balance, and even mitochondrial function, contributing to the energy metabolism of tumor cells (Owen et al. 2022). Additionally, mechanical forces generated by CAFs can alter tumor cell movement and morphology by activating cytoskeletal systems and intracellular signaling pathways, potentially accelerating tumor spread (Sharbeen et al. 2021). Exosomes, small extracellular vesicles secreted by cells, are critical mediators of cellular communication and tissue homeostasis (Pedersen et al. 2024). CAF-derived exosomes, in particular, play an essential role in influencing tumor behavior (Li et al. 2017; Shi et al. 2023). For example, Piwocka and colleagues found that exosomes secreted by CAFs carry microRNA-296-3p, which promotes malignant behaviors like proliferation, migration, invasion, and drug resistance in ovarian cancer cells. This suggests that microRNA-296-3p could serve as both a diagnostic marker and a therapeutic target (Sun et al. 2024a). Similarly, Zhang et al. discovered that miR-522, delivered via exosomes, enhances tumor cell resistance to chemotherapy and inhibits ferroptosis in gastric cancer cells by targeting ALOX15, thereby regulating lipid peroxidation (Zhang et al. 2020a). Their findings highlighted a novel intercellular pathway involving USP7, hnRNPA1, exo-miR-522, and ALOX15, which influences chemotherapy sensitivity through lipid peroxidation. Admittedly, CAFs contribute to the dense fibrotic stroma characteristic of many solid tumors (D'Aversa et al. 2024; Norton et al. 2020). This fibrosis not only physically impedes drug penetration, but also actively sequesters chemotherapeutic agents, significantly lowering their bioavailability and efficacy (D'Aversa et al. 2024). CAFs are prolific producers of growth factors like TGF-β, which not only enhances tumor cell proliferation and survival but also contributes to the creation of an immunosuppressive tumor microenvironment that shields the tumor from immune cell attack (Yang et al. 2023a; Perez-Penco et al. 2024). So recognizing the multifaceted roles of CAFs in mediating therapy resistance provides a strong rationale for developing CAF-targeted therapies (Timperi et al. 2024). Strategies that disrupt CAF functions or modify their interactions with tumor cells and other TME components could significantly enhance the efficacy of both conventional and immune-based cancer therapies (Xue et al. 2024; Eigentler et al. 2024). Conversely, tumors and tumor cells can influence CAF activation and function (Sung and Lee 2024). CAFs can be activated through direct interactions with tumor cells or via signaling pathways such as the Notch pathway. Once activated, CAFs remodel the ECM, which further amplifies their activation in a positive feedback loop (Park et al. 2020). Tumor cells may also induce the "reverse Warburg effect" in CAFs, enhancing glycolytic activity to meet the metabolic demands of the tumor. In pancreatic ductal adenocarcinoma (PDAC), for instance, tumor cells induce autophagy in CAFs, leading to the release of non-essential amino acids like alanine (Yang et al. 2023b). These amino acids support cancer cells by

fueling the tricarboxylic acid (TCA) cycle and lipid biosynthesis, aiding tumor growth and survival (Melissari et al. 2020).

In conclusion, the intricate relationship between CAFs, tumors, and tumor cells underscores the importance of CAFs as both therapeutic targets and integral components of cancer treatment strategies (Park et al. 2020). This interconnectedness suggests that future therapeutic approaches should be tailored based on the specific tumor type and CAF subtype, rather than relying on a one-size-fits-all approach (Li et al. 2021a; Esposito et al. 2024). Personalizing treatments in this way will help address the unique challenges posed by CAF–tumor interactions and improve the effectiveness of cancer therapies (Toledo et al. 2022; Jia et al. 2024a).

Cancer-associated fibroblasts: key regulators of the tumor microenvironment and tumor progression

The tumor microenvironment (TME) is a complex ecosystem composed of various cellular and non-cellular components, including ECM, blood vessels, immune cells, and tumor-associated cells (Timperi et al. 2024). CAFs are key players in this environment, interacting extensively with tumor cells and significantly contributing to tumorigenesis and progression (Schütz et al. 2023). Current research shows that CAFs can influence immune evasion by either activating or inhibiting the immune system (Peng et al. 2024; Li et al. 2023), as well as promoting angiogenesis, regulating inflammatory responses, and remodeling the ECM (Zeng et al. 2023a; Luo et al. 2022). These functions illustrate the crucial role of CAFs in shaping the TME, making the interaction between CAFs and the TME an essential focus for cancer research (Thinyakul et al. 2024).

CAF interactions within the TME are reciprocal. CAFs regulate the TME by secreting growth factors, chemokines, and other molecules that facilitate tumor formation and progression (Han et al. 2020a). For instance, CAFs secrete signaling molecules that remodel the ECM and reprogram metabolic pathways within the TME. This metabolic reprogramming supports tumor cell survival and growth, while the remodeling of the ECM enhances the structural environment necessary for tumor expansion (Cirri and Chiarugi 2012). Moreover, CAFs engage in transmembrane signaling with other cells in the TME, influencing disease progression through pathways such as PDGF, IL-6, and TNF-α (Fang et al. 2023; Piwocka et al. 2024). These chemokines attract and recruit immune cells and other cell types to the tumor site, further contributing to tumor growth and metastasis.

In recent years, the role of exosomes in the TME has gained attention, particularly in relation to cancer progression and inflammation (Liu et al. 2021). Exosomes are extracellular vesicles that facilitate communication between CAFs and tumor cells. These vesicles carry proteins, RNA, and other bioactive molecules that influence tumor development (Hajialiasgary Najafabadi et al. 2024; Cai et al. 2023). For example, research by Sun et al. demonstrated that exosomal non-coding RNAs (ncRNAs) secreted by CAFs contribute to the formation of the colorectal cancer microenvironment and are linked to resistance mechanisms in CRC patients undergoing radiotherapy (Sun et al. 2023). Exosomal communication is thus a critical pathway by which CAFs can influence tumor progression and treatment resistance.

Additionally, the TME influences the biological characteristics and functions of CAFs (Zhang et al. 2024a; Barros da Silva et al. 2024). For instance, environments with high concentrations of hyaluronic acid (HA) or oxidative stress can stimulate CAFs to exhibit more aggressive, tumor-promoting behavior (Donelan et al. 2022). These environmental factors can alter CAF activity, enhancing their ability to support tumor growth and metastasis. However, despite these insights, many uncertainties remain regarding how different TMEs affect CAF behavior (Liu et al. 2019b; Xu et al. 2023). Future research is expected to provide breakthroughs in understanding these complex interactions, which could lead to novel therapeutic strategies targeting CAFs and their interactions within the TME.

The role of cancer-associated fibroblasts in immune regulation within the tumor microenvironment

Immune cells are an important part of the tumor microenvironment and play complex roles in the development of cancer. These roles may sometimes have time-dependent dynamic transitions, such as the polarization of macrophages into different physiological phenotypes under different circumstances (Huang et al. 2021). In many cases, CAFs contribute to immune suppression, hindering the immune system's ability to attack tumor cells (Laplagne et al. 2019). This interaction between CAFs and immune cells is crucial for understanding how the tumor microenvironment supports cancer growth and evades immune surveillance. CAFs can interact with a variety of immune cells, including T cells, helper T cells, natural killer (NK) cells, macrophages, and myeloid-derived suppressor cells (MDSCs) (Thiery 2022; Huang et al. 2022a; Sharbeen et al. 2021; Tsoumakidou 2023). One prominent example of this interaction is how CAFs inhibit T cell activation. In a recent study, Ying et al. demonstrated that CAFs can express inhibitory receptors such as programmed death ligand 1 (PD-L1), which binds to PD-1 on T cells. This interaction effectively dampens the activation of T cells, allowing tumor cells to evade immune surveillance and proliferate unchecked (Ying et al. 2023). Similarly, Zeng et al. found that macrophages expressing M2 phenotype-related genes could enhance chemotherapy resistance in both CAFs and breast cancer cells, further promoting tumor survival and progression (Zeng et al. 2023b). In addition to T cells and macrophages, CAFs regulate cancer cell proliferation and migration by secreting extracellular signaling molecules such as growth factors and chemokines (Yavuz et al. 2020). These molecules recruit immune cells to the tumor site, where they often contribute to an immunosuppressive environment rather than promoting an effective anti-tumor response. However, the impact of CAFs on immune cells is not uniform (Jia et al. 2024b). Different CAF subtypes can influence the distribution and activity of immune cells in distinct ways, underscoring the importance of subtype-specific research in understanding the diverse roles of CAFs within the TME (Schütz et al. 2023).

Recent advances in spatial transcriptomics have provided deeper insights into the physical and functional relationships between CAFs and immune cells within tumors (Li et al. 2024d). For instance, Chen et al. used this technology to study lung cancer, revealing distinct distribution patterns of different cell types within the TME. They found that CAFs and malignant tumor cells often cluster together at the tumor core, while immune

cells, including macrophages and dendritic cells, are more commonly found at the tumor's periphery (Chen et al. 2023a). This spatial arrangement highlights the dynamic interplay between CAFs and immune cells and may help explain how immune suppression is maintained in certain regions of the tumor.

Nanomaterials and tumor targeted therapy

Classification of nanomaterials

In recent years, the rapid development of nanomaterials and their increasing applications in medicine have made medical nanomaterials a significant area of research (Lai et al. 2024; Meng et al. 2024). This review aims to explore various nanomaterials utilized in modern medicine, including nanoparticles, biomimetic nanoparticles, inorganic nanomaterials, organic–inorganic hybrid nanomaterials, and conventional nanomaterials, as well as their specific roles in biological systems (Table 1). At the same time, we also aim to clearly demonstrate the advantages and limitations of these nanomaterials in CAF targeting (Table 2; Fig. 2) Eleraky et al. (2020).

Tumor cells are influenced by various factors, including the TME and CAFs. Nanomaterials have shown the ability to either directly or indirectly disrupt tumor cell infiltration, invasion, and proliferation (Sun et al. 2024b). For example, a recent study demonstrated that gold–silver core–shell hybrid nanomaterials significantly inhibit the migration and proliferation of adenocarcinoma cells that are promoted by fibroblasts, effectively limiting metastatic spread (Kovács et al. 2020). Another experiment found that ZnO@CuS nanoparticles enhance tumor cell sensitivity to photothermal therapy by generating free radicals, which suppress cell migration (Deng et al. 2021). Additionally, the conjugation of monoclonal antibodies with nanomaterials offers highly targeted therapy that spares healthy tissue, and the combination of multiple drugs with nanomaterials opens new avenues in cancer treatment (Jiang et al. 2020). Radiotherapy and chemotherapy remain pivotal cancer treatments, with nanomaterials enhancing their efficacy (Liu et al. 2018; Goel et al. 2023; Jackson et al. 2023). Gold nanocages, when coupled with radioactive isotopes, enhance the effects of radiotherapy by forming radiolabeled marker (Qin et al. 2017). Nanoscale radiosensitizers have been observed to improve tumor cell sensitivity to radiation, thereby amplifying radiotherapy outcomes (Jain et al. 2024). Furthermore, nanomedicines, which are designed to carry chemotherapeutic agents, can target specific receptors on tumor cells, leading to increased drug accumulation and enhanced chemotherapy effectiveness (Cun et al. 2019). Nanomaterials also address the challenge of tumor drug resistance. Some nanoliposomes can prolong drug circulation, increasing bioavailability (Gu et al. 2021), while nanomicelles bind with multidrug resistance-associated proteins to facilitate drug entry into tumor cells (Edis et al. 2021; Hu et al. 2020b). Cheng et al. demonstrated that pH-sensitive gold nanocage conjugates can release anticancer drugs in response to acidic conditions, enhancing both drug concentration in tumor tissues and radiotherapy effectiveness (Chen et al. 2023b). Interestingly, several studies have shown that nanoparticles can cross the blood–brain barrier and modulate the TME, enhancing the efficacy of drugs for neurological conditions (Liang et al. 2022; Xu et al. 2022). This potential application of nanomedicines in neurological diseases remains a promising area of future research (D'Aversa et al. 2024; Krsek et al.

Table 1 Classification of nanomaterials

Classification	Material name	Role	Refs.
Nanoparticles	Gold nanoparticles (AuNPs)	Slow down the progression of pancreatic tumor in situ by affecting CAFs secretion	Hossen et al. (2019); Han et al. (2020b)
	Photosensitizers (such as zinc phthalocyanine, heme)	Release reactive oxygen species under light to kill cancer cells	Li et al. (2018a)
Biomimetic nanoparticles	Nanoparticles modified by protein or peptide	Inhibition of breast cancer metastasis	Gu et al. (2021); Singh et al. (2024b)
	Nanoparticles based on artificial collagen matrix		
	Artificial micro-robot inspired by bacteria		
Inorganic nanomaterials	Polyvinyl alcohol nanoparticles	Enhancing the efficacy of anti-tumor drugs	Gu et al. (2021); Liang et al. (2022); Xu et al. (2022); Singh et al. (2024b); Zhao and Rodriguez (2013)
	Ong chain polyethylene glycol nanoparticles		
	Polymeric nanomicelles		
	Polylactic acid, long-chain polyethylene glycol, polyvinyl alcohol, folate modified nanoparticles, liposome nanoparticles, pH-sensitive nanoparticles, heat sensitive nanoparticles, liposome nanoparticles with mitomycin on the surface		
	Ferritin	It can be used as a drug delivery system and shows great potential in cancer treatment	Li et al. (2018a)
	Graphene oxide	Killing cancer cells through a variety of mechanisms	Han et al. (2020b); Kim et al. (2017; Mauro et al. (2017)
	Quantum dots (QDs)	QDs conjugated with CAF-specific ligands can help visualize CAF distribution within the TME	Li et al. (2018a; Hou et al. (2021)
	Magnetic nanoparticles	Increasing the local concentration of therapeutic agent and reduce off-target effect Selectively damaging CAF and destroying ECM helps immune cells and drugs reach the tumor core more efficiently	Wang et al. (2023b); Ferraz et al. (2020); Mardhian et al. (2020)
	Gold nanoparticles (AuNPs)	AuNPs can be used for photothermal therapy Imaging enhancement, which can enhance contrast in CT scans	Yang et al. (2021); Ramesh et al. (2022); Hosseini et al. (2022)

Table 1 (continued)

Classification	Material name	Role	Refs.
Organic inorganic hybrid nanomaterials	Magnetic nanoparticles	It can be used as a drug delivery system and shows great potential in cancer treatment 30	Gu et al. (2021); Liang et al. (2022)
	Polymer nanomaterials	Killing cancer cells through a variety of mechanisms	Han et al. (2020b); Kim et al. (2017); Mauro et al. (2017)
	Liposome nanoparticles	Positioning and control, so as to be used for precise treatment and diagnosis of tumors	Zhu et al. (2023)
	Fatty acidified peptide nanoparticles	Enhancing the efficacy of anti-tumor drugs	Xu et al. (2022); Zhao and Rodriguez (2013); Fei et al. (2023); Ma et al. (2021); Qiu et al. (2019); Chattrairat et al. (2023); Kitano et al. (2021)
	Nanovesicle	Increase the accumulation of drugs in tumor tissues and reduce toxic and side effects	
	Nanowires	It can penetrate the blood–brain barrier, thus achieving the treatment of brain tumors	
	Nanotube	Directly interact with tumor cells, induce apoptosis or block their growth	
	Fibronectin (FN), transferrin receptor, integrin, MMP-2, TFR,	Regulate the levels of cytokines and chemokines in the tumor microenvironment, thereby affecting the movement and localization of tumor cells	Qin et al. (2017)
	Liposomes	Directly interact with tumor cells, induce apoptosis or block their growth	Chen et al. (2022)
	Drug-loaded nanospheres, drug-loaded nanotubes, drug-loaded nanovesicles	Targeting specific receptors on the surface of tumor cells to achieve selective killing of tumor cells	Duan et al. (2021; Fourniols et al. (2020)
Conventional nanomaterials	Polylactic acid, long-chain polyethylene glycol, polyvinyl alcohol, folate modified nanoparticles, liposome nanoparticles, pH-sensitive nanoparticles, heat sensitive nanoparticles, liposome nanoparticles with mitomycin on the surface	Increase the accumulation of drugs in tumor tissues and reduce toxic and side effects; PH sensitive nanoparticles can release drugs in acidic environment; thermosensitive nanoparticles can kill tumor cells by heating; Lipid with mitomycin on the surface	Gu et al. (2021); Liang et al. (2022); Xu et al. (2022); Zhao and Rodriguez (2013)

Table 2 Advantages and limitations of nanomaterials for CAF targeting

Nanomaterial type	Examples	Unique properties and advantages	Limitations
Organic	Liposomes, PLGA NPs	High biocompatibility, versatile drug/gene delivery	Limited imaging and lower physical stability
Inorganic	Iron oxide NPs, AuNPs, QDs	Magnetic and optical properties for targeted therapy and imaging	Potential toxicity, organ accumulation, complex clearance
Hybrid	Liposome-AuNPs, PLGA-coated Fe NPs	Enhanced stability, combined drug delivery and imaging (theranostics)	Complex synthesis, regulatory hurdles

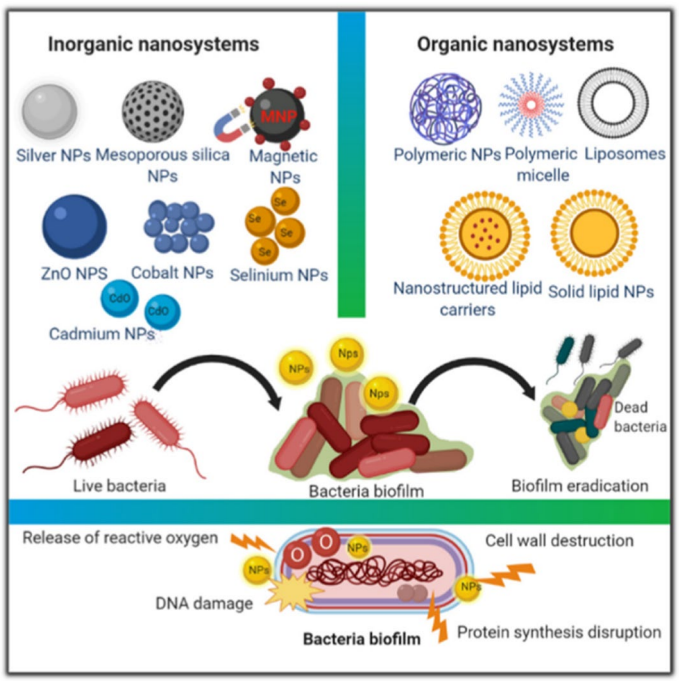

Fig. 2 Advancements in medical nanomaterials. Nanosystems can be classified into inorganic and organic types, based on their matrix characteristics and the materials they are composed of. This figure also focuses on the specific roles these nanomaterials play in managing bacterial biofilms. Furthermore, the title conveys the diversity of nanomaterial types discussed and their significant impact on biological systems. Reproduced from Eleraky et al. (2020), Copyright © 2020 by the authors

2024). Further, the intrinsic properties of inorganic nanomaterials can be harnessed to disrupt the physical structure of the ECM, commonly reinforced by CAFs (Fu et al. 2022; Seo et al. 2021). For example, magnetically guided nanoparticles can be directed to fibrotic regions of tumors to deliver therapeutics that specifically disrupt CAF functions (Guo et al. 2024a). Finally, inorganic nanomaterials are not limited to therapeutic applications, some also possess diagnostic capabilities, such as fluorescence and magnetic resonance imaging (MRI) (Ren et al. 2024; Cheng et al. 2024b). Magnetic nanoparticles, particularly those based on iron oxide, are extensively used in magnetic MRI due to their superb contrast enhancement capabilities (Ferrera et al. 2024; Guedes et al. 2024). Their magnetic properties also allow for precise control

and targeting when used with an external magnetic field, enhancing drug delivery efficiency to tumor sites, including those rich in CAFs (Hernández-Jiménez et al. 2022).

In conclusion, the application of nanomaterials in medicine continues to expand. However, while these materials offer significant promise, especially in cancer immunotherapy, there remain substantial challenges that must be addressed in future research.

Targeting cancer-associated fibroblasts with nanomaterials: therapeutic applications and mechanisms

Numerous previous studies have demonstrated that nanomaterials significantly affect CAFs (Li et al. 2018a), disrupting their functions and influencing the TME through various mechanisms (Wang et al. 2024d). On one hand, some nanomaterials serve as carriers for chemotherapeutic drugs or bioactive molecules, delivering them directly to CAFs (Huang et al. 2024a) and enhancing therapeutic efficacy while reducing off-target effects on healthy tissues (Geng et al. 2023). For instance, Li et al. developed reversibly bonded nanoparticles that can deliver anticancer drugs precisely to CAFs, illustrating their potential in targeted therapy (Yu et al. 2020). Additionally, Aljabali et al. highlighted that some nanomaterials possess immunomodulatory properties, facilitating the clearance or control of CAFs by modulating immune response (Aljabali et al. 2023).

Beyond drug delivery, specific nanomaterials directly target CAF-related molecular pathways to inhibit CAF activity (Zhou et al. 2021; Xin et al. 2021). For example, Zhou et al. developed a method using α-FAP-Z@FRT nanomaterials to target FAP on the surface of CAFs, this material selectively targets FAP expression in CAFs without affecting non-tumor tissues (Zhou et al. 2021). Moreover, different nanomaterials can affect CAFs in various ways. Further, gold-based nanomaterials, such as gold nanoparticles (GNPs) and gold nanocages, have demonstrated potential to modulate critical pathways within CAFs (Alhussan et al. 2022, 2021).For instance, Li et al. utilized a complex nanocomposite involving graphene oxide, gold nanoparticles, and fluorescent dyes, which was observed to release chemicals selectively to eliminate CAFs upon near-infrared laser irradiation (Yu et al. 2020). Additionally, certain nanomaterials function as carriers for photothermal therapy, generating heat upon exposure to light to induce apoptosis in CAFs (Li et al. 2018a). For instance, Mukherjee et al. demonstrated that 20 nm gold nanoparticles can transform CAFs into a quiescent state rich in lipids, inhibiting matrix deposition. Similarly, studies indicate that gold nanocages, nanoparticles, and nanorods can target and suppress CAF growth and function through photothermal effect (Hossen et al. 2019; Zheng et al. 2020). Specifically, gold nanocages disrupt CAF structures via photothermal therapy, impeding their proliferation and secretory function (Zheng et al. 2020), while gold nanoparticles selectively target CAFs to inhibit their proliferation and migration capabilities (Hossen et al. 2019). Nanomaterials offer unique capabilities for modulating key biochemical pathways within cancer-associated fibroblasts (Zhang et al. 2024b). Specific nanomaterials such as gold nanoparticles and liposomal formulations have been explored for their potential to interfere with TGF-β and IL-6 signaling pathways, pivotal in CAF-mediated tumor progression and immunosuppression (Pradhan et al. 2023; Zheng et al. 2023a). For instance, gold nanoparticles, when engineered to carry TGF-β inhibitors, target the fibrotic activity of CAFs (Yang et al. 2021; Zhang et al. 2021). By disrupting TGF-β signaling, these nanoparticles reduce the

fibroblastic activation and ECM deposition, which are crucial for tumor stroma formation and immunosuppression. Liposomal carriers encapsulating IL-6 siRNA effectively reduce the expression of IL-6 in CAFs (Zhang et al. 2024c; Dana et al. 2022). This reduction dampens the JAK/STAT signaling pathway, thereby mitigating the inflammatory and tumor-promoting activities of CAFs (Fang et al. 2023; Ahrens et al. 2017). Interestingly, recent research has shown that some nanomaterials can paradoxically promote the growth and function of CAFs, stimulating their proliferation and migration (Chen et al. 2023b; Fei et al. 2023). These findings may provide a new perspective for targeted treatment of CAFs and cancer immunotherapy. Moreover, we discovered that certain nanomaterials enable the detection of gene expression and products in CAFs, which could facilitate studies on their role in tumor development in the future (Cun et al. 2019). While these innovative ideas currently lack practical applications, they hold promise for future research and clinical applications.

Nanomaterials as modulators of cancer-associated fibroblasts in the tumor microenvironment

Research on how nanomaterials interact with CAFs within the TME is a key area in modern cancer therapy (Zhang et al. 2023c; Bromma et al. 2020). Nanomaterials modulate cellular-level biological activities within the TME due to their unique size and surface properties (Hu et al. 2022). These materials influence the behavior of CAFs either through direct physical interactions or by releasing specific chemical signals that promote or inhibit their pro-tumorigenic functions (Kovács et al. 2020). For instance, some nanomaterials alter the ECM composition, impacting the support that CAFs provide to tumor cell (Liu et al. 2019a; D'Aversa et al. 2024). To be specific, incorporating ECM-degrading enzymes like hyaluronidase or collagenase into nanocarrier designs can help break down the fibrous barrier, improving the penetration and distribution of nanoparticles within the tumor stroma (Chandrasekar et al. 2024; Qiu et al. 2024).

Nanomaterials within the TME not only serve as carriers for drugs and bioactive molecules (Yu et al. 2020; Yao et al. 2020). For example, specific nanomaterials regulate the availability of oxygen and nutrients, promoting apoptosis in tumor cells and subsequently reducing tumor volume (Qin et al. 2017; Yuan et al. 2021; Ruan et al. 2022). Hypoxia, a common feature in solid tumors, significantly affects the biochemical environment, altering the reactivity of nanomaterials (Song et al. 2024; Li et al. 2025). This can lead to premature degradation or deactivation of therapeutic agents carried by the nanoparticles, or it may change the way these materials are taken up by CAFs and other tumor cells (Wang et al. 2020). For example, developing nanomaterials that are activated by or responsive to hypoxic conditions can turn this TME characteristic into an advantage, triggering drug release or activation specifically in low-oxygen zones, thus targeting CAFs more effectively (Zhang et al. 2019; Zu et al. 2023). Additionally, these nanomaterials can modulate the immune system by targeting and activating various immune cells, thereby bolstering the immune response and enhancing the effectiveness of cancer therapies (Han et al. 2020b; Fei et al. 2023). Furthermore, nanomaterials exhibit therapeutic potential by regulating the roles of CAFs in immune responses, angiogenesis, and tumor tissue stiffening (Lu et al. 2024; Li et al. 2018b). For instance, certain

nanomaterials influence the physical and chemical dynamics of the TME. They disrupt angiogenesis in tumors and regulate the secretion of growth factors by tumor-associated fibroblasts, effectively inhibiting tumor growth and metastasis (Liang et al. 2022; Zhao and Rodriguez 2013).

Despite challenges such as targeting precision and potential off-target effects, current research focuses on enhancing nanomaterial design to overcome these issues (Kang and Li 2023). Overall, the interactions between nanomaterials and CAFs enrich our understanding of the complexity of the TME and open avenues for innovative anticancer strategies. However, further research and clinical trials are essential to optimize the use of nanomaterials and ensure their safety in clinical applications.

Immunomodulatory roles of nanomaterials targeting CAFs

CAFs play a central role in maintaining an immunosuppressive TME by recruiting and modulating immune cells through cytokine and chemokine secretion (Chandrasekar et al. 2024). Nanomaterials, when designed to target CAFs specifically, have the potential to disrupt this immune suppression and reprogram the TME to favor anti-tumor immune responses (Wang et al. 2023a; Shen et al. 2023). Although the diversity of nanomaterials leads them to be able to control the tumor immune microenvironment in a state of "activation" or "inhibition" by directly targeting specific cellular or molecular mechanisms, many materials are currently designed to target CAFs cells, which inhibit tumor immunity (Jian et al. 2024; Zhen et al. 2017; Zang et al. 2022).

Nanoparticles that specifically target CAFs, such as those delivering FAP- or α-SMA-targeted therapies, can significantly alter cytokine profiles within the TME (Rodponthukwaji et al. 2024; Priwitaningrum et al. 2016). By downregulating immunosuppressive cytokines, these nanoparticles can alleviate T-cell suppression, enhance T-cell activation, and potentially improve T-cell infiltration into the tumor (Liu and Zhao 2024; Wang et al. 2024e). For instance, in the study by zhou et al., liposomal nanoparticles loaded with TGF-β inhibitors have shown promise in reprogramming the TME, reducing the immunosuppressive signals that prevent effective T-cell responses (Zhou et al. 2024a). By diminishing CAF-mediated suppression, nanoparticles can improve the efficacy of immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors (An et al. 2023; Gong et al. 2021). Studies have shown that when CAF-targeting nanoparticles are combined with PD-L1 inhibitors, there is an increase in T-cell infiltration and activation within tumors (An et al. 2023; Tan et al. 2021). For example, gold nanoparticles conjugated with immune-modulatory ligands have been observed to enhance PD-1 blockade efficacy in melanoma models by reducing CAF-derived T-cell suppression (Cao et al. 2021). Further, CAFs often recruit and polarize macrophages toward an immunosuppressive M2 phenotype (Perez-Penco et al. 2024; Wei et al. 2024), which supports tumor growth and immune evasion (Tomassetti et al. 2024). However, nanoparticles targeting CAFs can disrupt this process by altering the CAF-derived cytokine environment (Pradhan et al. 2023), leading to a shift from M2 (immunosuppressive) to M1 (pro-inflammatory, anti-tumor) macrophage phenotypes (Gong et al. 2024). For instance, polymeric nanoparticles delivering IL-6 inhibitors to CAFs have demonstrated the ability to reduce M2 macrophage recruitment, reprogramming the TME to support a more inflammatory and immune-activating environment (Feng et al. 2024).

In addition, combining CAF-targeting nanomaterials with immune checkpoint inhibitors, such as PD-1 or PD-L1 inhibitors, represents a promising therapeutic strategy (Liu et al. 2024b). CAF-targeting nanoparticles can "prime" the TME by reducing immune suppression, creating a more receptive environment for immune checkpoint inhibitors to work effectively (Table 3). Studies have shown that pre-treatment with CAF-targeting nanoparticles such as TGF-β inhibitor-loaded liposomes, can decrease CAF-derived immunosuppressive factors and enhance T-cell infiltration (Zhen et al. 2017; Wang et al. 2024f). When followed by PD-L1 inhibitors, these primed tumors respond better, with increased T-cell activation and tumor regression observed in preclinical models of melanoma and lung cancer (Ou et al. 2022; Zhang et al. 2023d). In some studies, nanoparticles targeting CAFs have also been paired with chimeric antigen receptor T-cell (CAR-T) therapy (Dharani et al. 2024). By disrupting CAF-mediated barriers and reducing the immunosuppressive cytokine environment, CAF-targeting nanoparticles have been shown to improve CAR-T cell infiltration and efficacy in solid tumors (Zhang et al. 2023e; Liu et al. 2023b).

Tailoring nanomaterials to target CAF subtypes in cancer immunotherapy

Cancer-associated fibroblasts (CAFs) are a heterogeneous population of cells that exhibit distinct phenotypes and functions depending on the tumor context. The primary CAF subtypes identified in various cancers include myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) (Caramelo et al. 2023; Melchionna et al. 2023). Each subtype contributes differently to tumor progression, ECM remodeling, and immune modulation (Schütz et al. 2023; Chen et al. 2024a; Vaish et al. 2021). Consequently, a "one-size-fits-all" approach to targeting CAFs is inadequate, instead, nanomaterials must be tailored to interact with

Table 3 Summary of immunomodulatory effects and combination therapies

Targeted immune cell	Nanomaterial type	Mechanism of action	Combination strategy	Outcome	References
T cells	FAP-targeted liposomes, AuNPs	Downregulate TGF-β, IL-6	Combined with PD-L1 inhibitors	Enhanced T-cell infiltration, increased tumor regression	Lu et al. (2023); Feng et al. (2024); Zhang et al. (2023f); Orlowski et al. (2018)
Macrophages	Polymeric IL-6 inhibitor NPs	Shift M2 to M1 macrophage phenotype	Combined with immune checkpoint blockade	Increased pro-inflammatory macrophages, reduced immune suppression	Pradhan et al. (2023); Gong et al. (2024); Feng et al. (2024)
MDSCs	CCL2-inhibiting nanoparticles	Reduce MDSC recruitment	Pre-treatment for CAR-T therapy	Enhanced CAR-T cell infiltration and efficacy	Yang et al. (2021); Yazdimamaghani et al. (2025); Yong et al. (2019)
CAF/TME modulation	TGF-β inhibitor-loaded liposomes	Modulate cytokine environment, reduce CAF activation	Combined with PD-1 inhibitors	Improved checkpoint efficacy, reprogrammed TME	Lo et al. (2024); Cherukula et al. (2019); Vienot et al. (2022)

specific CAF subtypes to achieve optimal therapeutic effects (Zhang et al. 2024d; Yamamoto et al. 2023).

. Therefore, integrating tumor-specific CAF targeting into nanomaterial design can enhance the precision and therapeutic efficacy of nanomedicine.

Targeting myCAFs

myCAFs are characterized by the expression of α-smooth muscle actin (α-SMA) and are primarily involved in ECM production and stiffening, creating a physical barrier that hinders drug penetration and immune cell infiltration (Kearney et al. 2024). This CAF subtype is particularly abundant in desmoplastic tumors such as pancreatic and breast cancers (Burley et al. 2022; Zeltz et al. 2019). To specifically target myCAFs, nanoparticles can be functionalized with ligands or antibodies against α-SMA or other ECM-associated proteins highly expressed by myCAFs (Yang et al. 2021; Priwitaningrum et al. 2016). For instance, nanoparticles conjugated with α-SMA-targeting peptides have shown promise in preclinical studies by accumulating selectively within myCAF-rich regions, reducing ECM density, and enhancing therapeutic penetration (Zheng et al. 2023b). In a preclinical study by Tista Roy Chaudhuri and his colleagues, a nanoparticle platform conjugated with α-SMA-targeting antibodies demonstrated selective accumulation in myCAF-dense areas within pancreatic tumors in mouse models (Roy Chaudhuri et al. 2016). This targeted approach reduced ECM stiffness, improved immune cell infiltration, and synergized with immune checkpoint inhibitors, suggesting a promising strategy for desmoplastic tumors.

Targeting iCAFs

iCAFs are characterized by high levels of FAP and the secretion of pro-inflammatory cytokines such as IL-6 and IL-8 (Yang et al. 2023b; Kearney et al. 2024), which promote an immunosuppressive environment by recruiting immunosuppressive cells and supporting cancer cell survival (Liu et al. 2024c; Thorlacius-Ussing et al. 2024; Morgan et al. 2023). iCAFs are prevalent in tumors with a strong inflammatory component, such as melanoma and certain gastrointestinal cancers (Ran and Chen 2024; Agorku et al. 2024; Picard et al. 2023). Nanoparticles can be modified with FAP-specific ligands, antibodies, or small-molecule inhibitors to target iCAFs selectively (Rodponthukwaji et al. 2024; Zhang et al. 2024e). FAP-targeted nanoparticles have been shown to reduce the immunosuppressive influence of iCAFs by delivering payloads that either silence cytokine production or modulate immune cell recruitment (Zhao et al. 2024). FAP-targeted liposomes loaded with IL-6 and IL-8 siRNAs were shown to reduce pro-inflammatory cytokine levels in melanoma mouse models (Aslan et al. 2024; Barati et al. 2022), thereby diminishing immunosuppressive signaling within the TME and enhancing the efficacy of T-cell-based therapies (Salotto et al. 2022). This approach highlights the therapeutic potential of targeting iCAFs in inflammatory tumor environments.

Targeting apCAFs

apCAFs possess the unique ability to present antigens via MHC-II molecules but generally lack co-stimulatory signals, resulting in anergy or tolerance of T cells within the TME (Kerdidani et al. 2022; Macy et al. 2023). Targeting apCAFs is challenging but

potentially impactful, as modifying their interaction with immune cells could alter immune dynamics in favor of anti-tumor activity (No Author 2022; Macy et al. 2023). Nanoparticles designed to target MHC-II molecules or deliver agents that block inhibitory pathways within apCAFs could mitigate T-cell anergy (Srivastava et al. 2024; Liu et al. 2022b). For instance, nanomaterials conjugated with MHC-II blocking peptides or small molecules could reduce the suppressive effects of apCAFs on T-cell function, enabling more effective immune responses in tumors such as ovarian and gastric cancers where apCAFs are more prominent (Noureddine et al. 2023; Zheng et al. 2021). In ovarian cancer mouse models, MHC-II-targeted nanoparticles have been shown to interfere with apCAF-mediated T-cell anergy (Noureddine et al. 2023), thereby increasing T-cell activation and enhancing anti-tumor responses. Though in its early stages, this approach underscores the potential for highly specific targeting of CAF subtypes based on unique immune-modulatory properties.

Different tumor types in targeting strategies

The effectiveness of targeting strategies may vary significantly across different types of tumors (Table 4). For example, breast cancers with a high presence of iCAFs might benefit more from FAP-targeted therapies (Rodponthukwaji et al. 2024), while pancreatic cancers, characterized by dense stromal barriers predominantly formed by myCAFs, might be better addressed with α-SMA-targeted approaches (Ferraz et al. 2020; Roy Chaudhuri et al. 2016). Moreover, apCAFs play a notable role in ovarian cancer by inducing T-cell tolerance. Hence, MHC-II-targeted nanoparticles could be tailored to address T-cell anergy specifically in ovarian cancer models (Noureddine et al. 2023).

The role of CAF subtypes and their abundance can vary significantly between tumor types, necessitating tumor-specific targeting strategies (Huang et al. 2023, 2024b). However, by incorporating tumor-specific CAF targeting into nanomaterial design, we can enhance the precision of nanomedicine and improve therapeutic outcomes in a range of tumor microenvironments in the future.

Table 4 Recent examples in CAF subtype-targeting nanomaterials

CAF subtype	Marker	Nanomaterial type	Tumor model	Targeting strategy	Outcome	Refs.
myCAFs	α-SMA	α-SMA-targeted nanoparticle	Pancreatic, breast	ECM disruption	Increased immune cell infiltration and reduced ECM stiffness	Roy Chaudhuri et al. (2016); Zhang et al. (2024f)
iCAFs	FAP	FAP-targeted liposomes	Melanoma, GI cancer	Cytokine silencing	Reduced immunosuppression and enhanced T-cell response	Ran and Chen (2024); Agorku et al. (2024); Picard et al. (2023)
apCAFs	MHC-II	MHC-II-targeted nanoparticle	Ovarian	Immune modulation	Increased T-cell activation and reduced T-cell anergy	Noureddine et al. (2023; Marwedel et al. (2024)

Enhancing nanoscale drug delivery systems for targeting cancer-associated fibroblasts

Nanoscale drug delivery systems offer numerous advantages over traditional drug therapies (Wang et al. 2024b; Jia et al. 2021). However, challenges remain, particularly regarding their ability to effectively penetrate solid tumors, including proliferative connective tissue tumors (D'Aversa et al. 2024; Yunna et al. 2021). Therefore, it is essential to implement strategies that enhance the penetration and permeability of nanomedicines to improve drug delivery capabilities (Izci et al. 2022; Fang et al. 2020; Zhao et al. 2018). In this context, we present several enhanced delivery system approaches aimed at optimizing the targeting of CAFs within the TME (Fig. 3) Arranja et al. (2017).

Cutting-edge gene delivery approaches for targeting CAFs and tumor cells

Traditionally, the study of DNA and RNA has been fundamental in biology. In one study, researchers developed a polymer known as polymeric vinyl resin (PVR) and combined it with plasmids encoding relaxin (RLN) to form lipid nanoparticle complexes (LPPR), aiming to enhance gene transfer efficiency and reduce toxicity. This approach resulted in the inhibition of CAF proliferation and tumor growth (Zhang et al. 2023f). 5-Fluorouracil (5-FU), a DNA synthesis inhibitor, blocks the normal thymine nucleotide biosynthesis pathway, hindering the growth and division of tumor cells and CAFs; however, it also affects normal cells (Gong et al. 2023). In a study conducted by Handali and colleagues, a novel folate liposome was found to deliver fluorouracil more effectively to cancer cells while reducing toxicity (Handali et al. 2019). Similarly, Jain et al. discovered that a specific type of microRNA can enhance the sensitivity of colorectal cancer to radiotherapy by regulating tumor cell apoptosis and DNA damage repair pathways (Jain et al. 2024). In the research by Sheng et al., a CAF-targeted poly (lactic-co-glycolic acid) (PLGA) nanoemulsion was utilized to simultaneously deliver doxorubicin (DOX) and small interfering RNA (siRNA) targeting hepatocyte growth factor (HGF) for chemotherapy and gene therapy. Remarkably, the delivered siRNA reduced HGF expression in remaining CAFs, effectively overcoming chemotherapy-induced upregulation of HGF mRNA and preventing the increase of CAFs through an autocrine HGF feedback loop (Shen et al. 2023). These synergistic effects led to significant inhibition of tumor proliferation, migration, and invasion, as well as improved tumor permeability. In a nutshell, nanomaterials offer unique advantages when used in combination with traditional

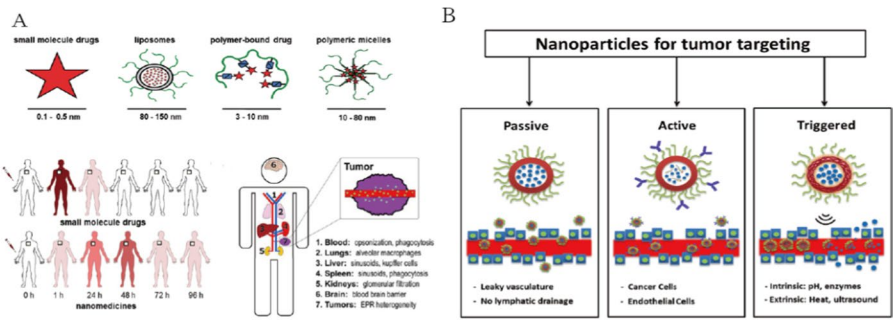

Fig. 3 **A** Nanomedicines and tumor targeting. Nanomedicines must overcome various barriers to achieve efficient tumor-targeted drug delivery. **B** Mechanisms of tumor targeting mediated by nanomedicine, passive, active, triggered. Reproduced from Arranja et al. (2017), Copyright © 2017 by the authors

cancer therapies such as chemotherapy, radiotherapy, and immunotherapy (Guo et al. 2023; Hou et al. 2019; Truffi et al. 2019). By facilitating targeted delivery and controlled release of therapeutic agents, nanomaterials can enhance treatment efficacy while potentially reducing systemic toxicity (Andoh et al. 2024; You et al. 2018). Nanoparticles such as liposomes and polymeric nanoparticles have been successfully used to encapsulate chemotherapeutic agents like docetaxel and doxorubicin, enhancing drug accumulation in tumor tissues and minimizing exposure to healthy cells (Beheshtizadeh et al. 2024; Xu et al. 2024a). Clinical trials have demonstrated that such nanoparticle formulations can significantly reduce cardiac toxicity commonly associated with doxorubicin (Chen et al. 2024b). Admittedly, nanoparticles designed to deliver cytokines such as IL-2 or checkpoint inhibitors such as PD-L1 blockers directly to the tumor microenvironment have shown promise in preclinical models (Zhang et al. 2023g; Chao et al. 2024). These strategies help to activate and sustain immune responses locally, potentially overcoming the immunosuppressive TME and leading to better clinical outcomes.

Furthermore, siRNA, a type of small RNA, can inhibit gene expression by interfering with the stability and translation of targeted mRNA molecules. Numerous studies have demonstrated that siRNA can be encapsulated within liposomes to inhibit gene expression in tumor cell (Pei et al. 2019; Sohn 2020). However, there are only a few studies showing that siRNA may also act on CAFs to inhibit their biological functions (Suh et al. 2020; Hu et al. 2024b), indicating a need for further research in this area. Lastly, researchers have developed a dual-labeled nanoprobe based on small extracellular vesicles (sEVs) that can be used for tumor detection and diagnosis (Santos-Coquillat et al. 2022). This technology also has potential as a valuable tool for studying the biological behaviors of nanosystems in drug delivery, which we believe holds significant application value for future research.

Applications of small-molecule drugs and their carriers in targeting cancer-associated fibroblasts

Currently, numerous small-molecule drugs are utilized in cancer treatment and to improve TME (Liu et al. 2019a; Bromma et al. 2020). This highlights the advantages of small-molecule drugs in targeting CAFs and contributing to cancer immunotherapy. In this section, we summarize recent advancements in small molecule-loaded drug delivery systems designed to target CAFs.

Nanodrug carriers, such as Cellax-DTX nanoparticles, deliver chemotherapy drugs with high specificity to CAFs, promoting their apoptosis and modulating the TME (Ernsting et al. 2015). Furthermore, Sitia and colleagues developed functionalized H-ferritin nanocages combined with fragments of fibroblast activation protein (FAP) antibodies, creating highly specific drug carriers with strong affinity for CAFs (Sitia et al. 2021). Similarly, Duan designed a dual-targeted liposome-hybrid micelle system (RPM@NLQ) triggered by matrix metalloproteinase (MMP), which sequentially delivers quercetin (Que) and paclitaxel (PTX) to CAFs. This system downregulates Wnt16 expression in CAFs, thus enhancing fibrosis reduction (Duan et al. 2022). Additionally, a specialized nanoemulsion (NE) system has been developed to deliver the anti-fibrotic drug fraxinellone (Frax) to CAFs (Santos-Coquillat et al. 2022). Researchers observed that Frax NE, when combined with tumor-specific peptide vaccines, may represent an effective and

safe treatment strategy (Santos-Coquillat et al. 2022). Other small-molecule compounds, such as superparamagnetic iron oxide nanoparticles (SPIONs), target fibroblast growth factor 2 (FGF2) precursors in CAFs, inhibiting their production and enhancing the efficacy of gemcitabine (Mardhian et al. 2020).

Clara et al. demonstrated that hydrogen peroxide plays a crucial role in the interaction between gold–iron alloy nanoparticles and CAFs (Faria et al. 2023). Additionally, some macromolecular systems, such as the nano-composite hydrogel developed by Liu et al., and the peptide–doxorubicin (GFLG–DOX) conjugate of polyamidoamine (PAMAM) dendritic macromolecules designed by Rashed M et al., have shown the potential to improve chemotherapy drug penetration and efficacy without harming healthy tissues (Liu et al. 2019c; Almuqbil et al. 2020).

Innovative strategies for targeting cancer-associated fibroblasts in immunotherapy

Targeting CAFs has emerged as a critical strategy in cancer immunotherapy. Recent advances have led to the development of antibodies and other ligands that specifically bind to receptors on the surface of CAFs, inducing their apoptosis or inhibiting their proliferation. For instance, Liang et al. developed a peptide-assembled nanosystem that effectively inhibits CAF metastasis and prostate cancer progression (Lang et al. 2019). Additionally, strategies to reprogram CAFs are being explored. One such approach involves metabolic reprogramming, where the regulation of glucose uptake and lactate production forms the basis for new drug-targeting strategies (Li et al. 2021b; Becker et al. 2020). For example, Theivendran et al. utilized DMON-P to reprogram CAFs, downregulating CAF-specific biomarkers and successfully delivering doxorubicin (Dox) to inhibit tumor growth (Theivendran et al. 2024). Furthermore, DNA-targeted vaccines show great promise in CAF-targeted immunotherapy (Geng et al. 2019). Geng et al. developed a vaccine targeting both fibroblast activation protein alpha (FAPα) and the tumor antigen survivin, which not only eliminated CAFs, but also regulated the tumor microenvironment, thereby enhancing T-cell-mediated anticancer effect (Geng et al. 2020). Another notable study by Hu and colleagues involved the use of CAFs as antigens to create vaccines that stimulated an immune response specifically targeting CAFs. Their experiments showed success in both in vitro and in vivo models, demonstrating the feasibility of using CAFs as vaccine antigens in cancer therapy, a concept that warrants further exploration (Hu et al. 2024b). Moreover, activated T-cell therapies are also gaining attention. One study introduced activated T cells into the tumor site, where they specifically targeted CAFs, leading to reduced tumor growth (Pei et al. 2019). Liposomes serve as effective carriers for CAF-targeted therapies as well. For instance, Li et al. conjugated single-chain variable fragment (scFv) antibodies to liposomes, utilizing the high-affinity binding of monoclonal antibodies to enhance the penetration of liposomes into tumor tissues, thereby improving the efficacy of colorectal cancer treatment (Li et al. 2021c). Furthermore, a novel co-loaded liposome targeting the insulin receptor (IR) was shown to reduce CAF activity, thus inhibiting tumor progression (Sun et al. 2024c). In another study, Lee et al. used the anti-fibrotic drug nintedanib to decrease CAF activation and proliferation. Nintedanib was found to block the platelet-derived growth factor receptor beta (PDGFRβ) signaling pathway, reducing the secretion of interleukin-6 (IL-6) and thereby inhibiting CAF function (Lee 2023).

Nanomaterials in clinical trials

While preclinical studies have demonstrated the promise of nanomaterials in targeting CAFs and modulating the TME, translating these findings into clinical practice presents significant challenges. Here, we review the current status of nanomaterial-based therapies in clinical trials and discuss specific nanomaterials that have progressed to advanced preclinical or clinical trial phases, as well as the challenges they face in clinical translation (Table 5). Gold nanoparticles, for instance, have been tested in Phase I/II trials for their efficacy in targeting tumor microenvironments without adverse systemic effects (Sun et al. 2024d; Dai et al. 2018). Liposome-based therapies have also reached clinical trials, showcasing potential in targeted drug delivery to reduce tumor resistance (Li et al. 2024e; Zhang et al. 2024g). Liposomal formulations, such as Doxil (doxorubicin encapsulated in liposomes), have already been approved for cancer therapy and have inspired further development of liposome-based therapies in cancer immunotherapy (Xu et al. 2024b). Liposomes can encapsulate immunotherapeutics and target them to specific cells within the TME, improving treatment specificity and reducing systemic toxicity (Chen et al. 2016). Poly (lactic-co-glycolic acid) (PLGA) nanoparticles are widely used in drug delivery due to their biocompatibility and ability to encapsulate both hydrophobic and hydrophilic drugs (Shen et al. 2023; Ye et al. 2020). Clinical trials are ongoing to

Table 5 Key nanomaterial-based therapies currently in clinical trials

Nanomaterial type	Therapy name (if available)	Clinical trial phase	Cancer targeted	Mechanism of action	Refs
Liposomes	Doxil	Approved	Liver cancer, breast	Encapsulation of doxorubicin for tumor targeting and reduced toxicity	Xu et al. (2024b); Zhao et al. (2020)
Liposomes	Pembrolizumab-liposome	Phase II	Melanoma, NSCLC	Delivery of checkpoint inhibitor for improved immune activation	Sui et al. (2024); Zhang et al. (2013)
Polymeric nanoparticles	PLGA-paclitaxel	Phase I/II	Melanoma, rectal cancer	Controlled release of paclitaxel to reduce systemic side effects	Shen et al. (2023); He et al. (2024)
Gold nanoparticles	AuNP-IL-12 conjugate	Preclinical	Pancreatic, breast	Direct immune modulation by targeting CAFs and promoting immune cell infiltration	Agarwal et al. (2024); Luo et al. (2024a)
Iron oxide nanoparticles	Ferumoxytol	Phase II	Brain, liver	MRI-guided delivery and hyperthermia-induced tumor suppression	Cristofolini et al. (2020); Nicolás-Boluda et al. (2020)
Dendrimers	Dendrimer-methotrexate	Phase I	Leukemia, lymphoma	Controlled release to minimize toxicity and enhance tumor targeting	Feeney et al. (2022); Palombarini et al. (2021)

assess the efficacy of PLGA nanoparticles in delivering checkpoint inhibitors directly to tumors, which could increase immune activation within the TME.

One of the primary challenges in nanomedicine is ensuring biocompatibility and minimizing toxicity (Chandrasekar et al. 2024; Damani et al. 2024; Xu et al. 2024c). For instance, while liposomes and PLGA nanoparticles have generally favorable biocompatibility profiles (Mirza-Aghazadeh-Attari et al. 2022; Ali et al. 2021), other nanomaterials, such as metal nanoparticles, can induce oxidative stress or accumulate in organs, posing risks of long-term toxicity (Kahil et al. 2024; Liang et al. 2024b). In addition, efficiently delivering nanomaterials to CAFs and other TME components remains difficult (Zheng et al. 2023a). The dense ECM created by CAFs can act as a physical barrier, limiting the penetration of nanoparticles into tumor tissues (Zhang et al. 2024f; Ye et al. 2024). Techniques like size optimization and ligand-mediated targeting are being explored to improve intratumoral delivery and CAF specificity (Singh et al. 2024a; Kaps and Schuppan 2020). However, advancements in nanotechnology and regulatory science are expected to address these hurdles, enhancing the translational pathway for nanomaterials in cancer therapy (Luo et al. 2024; Guo et al. 2024b; Chen et al. 2024c). Continued collaboration between researchers, clinicians, and regulatory bodies is crucial to harness the full potential of nanomedicine.

Conclusion and future perspectives research

The past decades has consistently highlighted the multifaceted role of CAFs in tumor development and progression. CAFs not only contribute to the formation of the ECM that constitutes the tumor stroma, but also secrete growth factors, chemokines, exosomes, and metabolites that influence virtually all aspects of tumor biology, including drug resistance and treatment responses (Rizzolio et al. 2022). As scientific understanding of CAFs deepens, novel avenues for targeted immunotherapy based on their unique properties are emerging. A growing body of evidence suggests a significant correlation between programmed death-ligand 1 (PD-L1) expression levels and the degree of CAF infiltration in tumors. Certain CAF subsets have been shown to suppress T-cell activity by secreting PD-L1, thereby aiding tumor cells in evading immune detection and destruction (Yin et al. 2023; Choueiri et al. 2021; Gorchs et al. 2020). This highlights the importance of further research into the interplay between PD-L1 and CAFs to unravel the regulatory mechanisms underlying the tumor immune microenvironment. Understanding these mechanisms will be pivotal for developing more effective immunotherapies that can enhance the body's ability to combat tumors. Moreover, CAFs exert a direct influence on tumor cell behavior and characteristics through the secretion of growth factors, the activation of protein receptor signaling pathways, and the modulation of gene expression. Targeting these critical pathways may offer a promising strategy for combating cancer. Here, we summarize key drugs and therapies currently under investigation or in clinical use that aim to inhibit the pro-tumorigenic functions of CAFs (Table 6).

Table 6 provides a comprehensive overview of key targets and therapeutic strategies involving CAFs, highlighting innovative approaches in cancer immunotherapy. It enumerates targets like PD-L1, TGF-β, and IGF-1 critical in modulating CAF activity within the tumor microenvironment. Innovative strategies include monoclonal antibodies such as adebrelimab targeting PD-L1 to enhance T-cell-mediated immune responses,

Table 6 Key targets and therapeutic strategies involving CAFs

Target	Function	Drug	Mechanism	Preclinical or clinical trials	Refs.
PD-L1	Promote T cell mediated	Adebrelimab (A humanized monoclonal antibody with high affinity)	PD-L1 antibody	Phase II	Yin et al. (2023)
PD-L1 AND VEGFR	Inhibition of tumor escape and angiogenesis	Avelumab and axitinib	PD-L1 antibody AND tyrosine kinase inhibitor (TKI)	Phase III	Choueiri et al. (2021)
TGF-β	Inhibit CAFs activation	Galunisertib	Active inhibitor	Phase II	Faivre et al. (2019)
TGFb	Inhibition of autologous lipase activity	Autogenous lipase inhibitor IOA-289	Active inhibitor	Preclinical	Pietrobono et al. (2024)
IGF-1	Blocking the signal transduction between IGF-1 and its receptor	An inhibitor	Active inhibitor	Preclinical	Spandau et al. (2021)
FGFR2	Attenuate tumor activity	Futibatinib	FGFR1-4 inhibitor	Phase I	Goyal et al. (2023)
Pin1	Antibody binding to CAF	DNA encoding microcapsule system (DMS)	Pin1 inhibitor/ active inhibitor	Preclinical	Liu et al. (2022c)
Zinc finger binding protein 1 (ZBP1)	Inhibition of tumor growth and metastasis by inhibiting mTOR signaling pathway	CBL0137	A small-molecule compound/activator	Preclinical	Zhang et al. (2022a)
Hypoxia inducible factor 1, 2 (HIF1、2)	Specifically cleave DNA sequences	CRISPR-Cas9	Dual enzyme system	Preclinical	Garcia (2022)
HIF2	Inhibit hif2, inhibit cancer cells	Belzutifan	A small-molecule compound/ active inhibitor	Phase III	Garcia (2022)
Wnt2 molecule	Enhance the efficacy of ICI	Anti Wnt2 monoclonal antibody	Anti Wnt2 monoclonal antibody	Preclinical	Huang et al. (2022b)
Integrin αvβ3	Inducing apoptosis of triple negative breast cancer cells	ProAgio	Protein	Preclinical	Sharma et al. (2021)
Galectin-1 (Gal-1)	Downregulated the production of plasminogen activator inhibitor 2 (PAI-2)	Therapeutic inhibitors (LLS30)	Active inhibitor	Preclinical	Tsai et al. (2022)
CAFs and T cells	Reduce the proliferation and migration of fibroblasts and reduce inflammation	Calcipotriol	Vitamin D analogs	Phase II	Gorchs et al. (2020)

and inhibitors like galunisertib aimed at suppressing CAF activation by inhibiting TGF-β. Small-molecule inhibitors and therapeutic antibodies explore potential in attenuating CAF-induced tumor activities, suggesting novel avenues for precision medicine

in diverse cancer treatments. These strategies underscore the importance of targeting CAFs to disrupt their pro-tumorigenic functions and enhance therapeutic outcomes.

While nanomaterials can modulate immune responses and enhance drug delivery, their interaction within the complex TME requires a deeper understanding to avoid unintended immunosuppressive effects (D'Aversa et al. 2024; Chen et al. 2016; Mardhian et al. 2018; Avgoustakis and Angelopoulou 2024). Moreover, the safety of nanomaterials—particularly in terms of biodegradability and long-term toxicity—remains a major concern, necessitating rigorous clinical validation (Yuan et al. 2023; Mu et al. 2021; Kesharwani et al. 2024). The prolonged presence of nanoparticles in the body may lead to unforeseen complications, requiring careful management of these risks (Mardhian et al. 2018; Zhang et al. 2024h; Lee et al. 2024). Despite these challenges, nanomaterials offer revolutionary potential in cancer therapy (Dasgupta et al. 2023). Future research should focus on overcoming these limitations through the development of more specific, efficient, and biocompatible nanomaterials (Zheng et al. 2022; Zhang et al. 2022b; Affinito et al. 2024; Tan et al. 2022). This includes improving delivery systems, exploring combination therapies, and enhancing our understanding of the TME (Sung and Lee 2024; Tang et al. 2021; Mu et al. 2024; Choi et al. 2024). A promising avenue involves the development of dual-functional nanomaterials that target both CAFs and immune checkpoints, which could reactivate the immune system while disrupting the supportive TME (Geng et al. 2023; Liu et al. 2024b). Moreover, we recently discovered that some studies have explored the application of traditional Chinese medicine ingredients in targeted delivery, which represents another effective treatment method (Zheng et al. 2023a; Zhang et al. 2020b) However, due to limited current research, there is not sufficient data to extensively discuss this system.

Scaling up the production of nanomaterials while maintaining stringent quality and safety standards remains a critical challenge in advancing them from the laboratory to clinical settings (Pednekar et al. 2024). Regulatory approval processes are also complex due to the novel properties of nanomaterials, requiring tailored assessment protocols (Singh et al. 2024a, 2024b; Tagaras et al. 2024). Precision engineering of nanomaterials and advanced targeted delivery systems could help address these challenges (Kesharwani et al. 2024; Liu et al. 2024d; Zheng et al. 2024). Moreover, developing combination therapies that incorporate nanomaterials may maximize therapeutic efficacy while minimizing side effects by enabling lower dosages and more targeted action (Chen et al. 2024d; Zare et al. 2024; Overchuk et al. 2023).

To overcome these hurdles, interdisciplinary collaboration between researchers, clinicians, and regulatory bodies will be crucial (Han and Santos 2024; Cheng et al. 2024c). Integrating emerging technologies such as machine learning for predictive modeling of nanomaterial interactions within the TME could accelerate the development of effective therapies (Gao et al. 2024; Leong et al. 2021). Additionally, artificial intelligence (AI) could revolutionize nanomaterial design by optimizing nanoparticle properties for enhanced delivery and efficacy based on vast datasets that identify biomarkers (Gao et al. 2024; Bag et al. 2024; Mahajan and Bhattacharya 2024). In parallel, green nanomaterials, designed with sustainability in mind, offer an eco-conscious alternative for cancer treatment (Zhou et al. 2024b; Yang et al. 2023c). These materials utilize biodegradable components that pose minimal risk to the environment and

human health (Montazersaheb et al. 2024; Balčiūnaitienė et al. 2022). Their biocompatibility and reduced toxicity make them ideal candidates for long-term therapeutic applications, contributing to both patient outcomes and global sustainability goals (Naseer et al. 2022; Zhong et al. 2021; Zhang and Ge 2020).

Abbreviations

CAFs	Cancer-associated fibroblasts
TME	Tumor microenvironment
CRC	Colorectal cancer
ECM	Extracellular matrix
myCAFs	Myofibroblasts
iCAFs	Inflammatory CAFs
apCAFs	Antigen-presenting CAFs
MSCs	Marrow-derived mesenchymal stem cells
TGFβ	Transforming growth factor beta
IL-6	Interleukin-6
α-SMA	Alpha-smooth muscle actin
FAP	Fibroblast activation protein
PDGFR	Platelet-derived growth factor receptor
FN	Fibronectin
LN	Laminin
MMPs	Matrix metalloproteinases
EPCAM	Epithelial cell adhesion molecule
SGR	Synovial glycoprotein
MBL	Mannose-binding lectin
OPN	Osteopontin
HGF	Hepatocyte growth factor
PDAC	Pancreatic ductal adenocarcinoma
TNF-α	Tumor necrosis factor-alpha
MDSCs	Myeloid-derived suppressor cells
PD-L1	Programmed death ligand 1
AuNPs	Gold nanoparticles
TRF	Transferrin receptor
MMP-2	Matrix metalloproteinase-2
PVR	Polymeric vinyl resin
RLN	Relaxin
LPPR	Lipid nanoparticle complexes
5-FU	5-Fluorouracil
PLGA	Poly (lactic co-glycolic acid)
DOX	Doxorubicin
sEVs	Small extracellular vesicles
Que	Quercetin
FGF 2	Fibroblast growth factor 2
NE	Nanoemulsion
SPIONs	Superparamagnetic iron oxide nanoparticles
PAMAM	Polyamidoamine
IR	Insulin receptor
TKI	Tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor
PAI-2	Plasminogen activator inhibitor 2
HIF 1	Hypoxia inducible factor 1
ICI	Immune checkpoint inhibitor
ZBP1	Zinc finger binding protein 1
miR	MicroRNA
NK cells	Natural killer cells
TCA cycle	Tricarboxylic acid cycle
USP7	Ubiquitin-specific processing protease 7
hnRNPA1	Heterogeneous nuclear ribonucleoprotein A1
ALOX15	Arachidonate 15-lipoxygenase
QDs	Quantum dots
AI	Artificial intelligence

Author contributions

Both ZSZ and LC participated in the conceptualization of the article topic. The chart was completed by ZSZW, the manuscript was completed by ZSZ, and LC checked the manuscript. All authors have reviewed the manuscript.

Funding
This study was supported by Natural Science Foundation of Sichuan Province (2023NSFSC1552), University-Level Natural Science Foundation General Project of Chengdu Medical College (2024CDYXY-01) , Clinical Science Research Foundation of Chengdu Medical College and the First Affiliated Hospital of Chengdu Medical College (24LHLNYX1-08), Clinical Science Research Foundation of Chengdu Medical College and Nanbu People's Hospital (2024LHFBM1-04), Clinical Science Research Foundation of Chengdu Medical College and the Third Affiliated Hospital of Chengdu Medical College (2024LHFYSZ1-41).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors consent for publication.

Competing interests
The authors declare no competing interests.

Received: 21 October 2024 Accepted: 16 December 2024
Published online: 17 January 2025

References

Affinito A, Quintavalle C, Chianese RV et al (2024) MCT4-driven CAF-mediated metabolic reprogramming in breast cancer microenvironment is a vulnerability targetable by miR-425-5p. Cell Death Discov 10(1):140. https://doi.org/10.1038/s41420-024-01910-x

Agarwal H, Bynum RC, Saleh N et al (2024) Theranostic nanoparticles for detection and treatment of pancreatic cancer. Wiley Interdiscip Rev Nanomed Nanobiotechnol 16(4):e1983. https://doi.org/10.1002/wnan.1983

Agorku DJ, Bosio A, Alves F, Ströbel P, Hardt O (2024) Colorectal cancer-associated fibroblasts inhibit effector T cells via NECTIN2 signaling. Cancer Lett 595:216985. https://doi.org/10.1016/j.canlet.2024.216985

Alhussan A, Bromma K, Perez MM et al (2021) Docetaxel-mediated uptake and retention of gold nanoparticles in tumor cells and in cancer-associated fibroblasts. Cancers 13(13):3157. https://doi.org/10.3390/cancers13133157

Alhussan A, Palmerley N, Smazynski J et al (2022) Potential of gold nanoparticle in current radiotherapy using a co-culture model of cancer cells and cancer associated fibroblast cells. Cancers 14(15):3586. https://doi.org/10.3390/cancers14153586

Ali S, Amin MU, Tariq I et al (2021) Lipoparticles for synergistic chemo-photodynamic therapy to ovarian carcinoma cells: in vitro and in vivo assessments. Int J Nanomed 16:951–976. https://doi.org/10.2147/IJN.S285950

Aljabali AA, Obeid MA, Bashatwah RM et al (2023) Nanomaterials and their impact on the immune system. Int J Mol Sci 24(3):2008. https://doi.org/10.3390/ijms24032008

Almuqbil RM, Heyder RS, Bielski ER, Durymanov M, Reineke JJ, da Rocha SRP (2020) Dendrimer conjugation enhances tumor penetration and efficacy of doxorubicin in extracellular matrix-expressing 3D lung cancer models. Mol Pharm 17(5):1648–1662. https://doi.org/10.1021/acs.molpharmaceut.0c00083

An EK, Zhang W, Park HB et al (2023) Immunosuppressive nanoparticles containing recombinant PD-L1 and methotrexate alleviate multi-organ inflammation. Biomaterials 301:122233. https://doi.org/10.1016/j.biomaterials.2023.122233

Andoh V, Ocansey DKW, Naveed H et al (2024) The advancing role of nanocomposites in cancer diagnosis and treatment. Int J Nanomed 19:6099–6126. https://doi.org/10.2147/IJN.S471360

apCAFs are derived from mesothelial cells and induce regulatory T cells. Cancer Discov. 2022;12 (7):1609. https://doi.org/10.1158/2159-8290.CD-RW2022-085.

Arranja AG, Pathak V, Lammers T, Shi Y (2017) Tumor-targeted nanomedicines for cancer theranostics. Pharmacol Res 115:87. https://doi.org/10.1016/j.phrs.2016.11.014

Aslan M, Ozturk S, Shahbazi R et al (2024) Therapeutic targeting of siRNA/anti-cancer drug delivery system for non-melanoma skin cancer. Part I: Development and gene silencing of JAK1siRNA/5-FU loaded liposome nanocomplexes. Eur J Pharm Biopharm off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV. 203:114432. https://doi.org/10.1016/j.ejpb.2024.114432

Avgoustakis K, Angelopoulou A (2024) Biomaterial-based responsive nanomedicines for targeting solid tumor microenvironments. Pharmaceutics 16:179

Bag A, Ghosh G, Sultan MJ, et al. Bio-inspired sensory receptors for artificial-intelligence perception. Adv Mater Deerfield Beach Fla. 2024:e2403150. https://doi.org/10.1002/adma.202403150.

Balčiūnaitienė A, Štreimikytė P, Puzerytė V et al (2022) Antimicrobial activities against opportunistic pathogenic bacteria using green synthesized silver nanoparticles in plant and lichen enzyme-assisted extracts. Plants Basel Switz 11(14):1833. https://doi.org/10.3390/plants11141833

Barati M, Mirzavi F, Nikpoor AR et al (2022) Enhanced antitumor immune response in melanoma tumor model by anti-PD-1 small interference RNA encapsulated in nanoliposomes. Cancer Gene Ther 29(6):814–824. https://doi.org/10.1038/s41417-021-00367-9

Barros da Silva P, Oliveira RJA, Araújo M, Caires HR, Bidarra SJ, Barrias CC (2024) An integrative alginate-based 3D in vitro model to explore epithelial-stromal cell dynamics in the breast tumor microenvironment. Carbohydr Polym 342:122363. https://doi.org/10.1016/j.carbpol.2024.122363
Bartoschek M, Oskolkov N, Bocci M et al (2018) Spatially and functionally distinct subclasses of breast cancer-associated fibroblasts revealed by single cell RNA sequencing. Nat Commun 9(1):5150. https://doi.org/10.1038/s41467-018-07582-3
Bates ME, Libring S, Reinhart-King CA (2023) Forces exerted and transduced by cancer-associated fibroblasts during cancer progression. Biol Cell 115(8):e2200104. https://doi.org/10.1111/boc.202200104
Becker LM, O'Connell JT, Vo AP et al (2020) Epigenetic reprogramming of cancer-associated fibroblasts deregulates glucose metabolism and facilitates progression of breast cancer. Cell Rep 31(9):107701. https://doi.org/10.1016/j.celrep.2020.107701
Beheshtizadeh N, Amiri Z, Tabatabaei SZ et al (2024) Boosting antitumor efficacy using docetaxel-loaded nanoplatforms: from cancer therapy to regenerative medicine approaches. J Transl Med 22(1):520. https://doi.org/10.1186/s12967-024-05347-9
Bromma K, Bannister A, Kowalewski A, Cicon L, Chithrani DB (2020) Elucidating the fate of nanoparticles among key cell components of the tumor microenvironment for promoting cancer nanotechnology. Cancer Nanotechnol 11(1):8. https://doi.org/10.1186/s12645-020-00064-6
Burley A, Rullan A, Wilkins A (2022) A review of the biology and therapeutic implications of cancer-associated fibroblasts (CAFs) in muscle-invasive bladder cancer. Front Oncol 12:1000888. https://doi.org/10.3389/fonc.2022.1000888
Cai CS, He GJ, Xu FW (2023) Advances in the applications of extracellular vesicle for the treatment of skin photoaging: a comprehensive review. Int J Nanomed 18:6411–6423. https://doi.org/10.2147/IJN.S433611
Cao Y, Ding S, Zeng L et al (2021) Reeducating tumor-associated macrophages using CpG@Au nanocomposites to modulate immunosuppressive microenvironment for improved radio-immunotherapy. ACS Appl Mater Interfaces 13(45):53504–53518. https://doi.org/10.1021/acsami.1c07626
Caramelo B, Zagorac S, Corral S, Marqués M, Real FX (2023) Cancer-associated fibroblasts in bladder cancer: origin, biology, and therapeutic opportunities. Eur Urol Oncol 6(4):366–375. https://doi.org/10.1016/j.euo.2023.02.011
Chandrasekar V, Panicker AJ, Dey AK et al (2024) Integrated approaches for immunotoxicity risk assessment: challenges and future directions. Discov Toxicol 1(1):9. https://doi.org/10.1007/s44339-024-00010-w
Chao PH, Chan V, Li SD (2024) Nanomedicines modulate the tumor immune microenvironment for cancer therapy. Expert Opin Drug Deliv 21:1719. https://doi.org/10.1080/17425247.2024.2412245
Chattrairat K, Yasui T, Suzuki S et al (2023) All-in-one nanowire assay system for capture and analysis of extracellular vesicles from an ex vivo brain tumor model. ACS Nano 17(3):2235–2244. https://doi.org/10.1021/acsnano.2c08526
Chen B, Dai W, Mei D et al (2016) Comprehensively priming the tumor microenvironment by cancer-associated fibroblast-targeted liposomes for combined therapy with cancer cell-targeted chemotherapeutic drug delivery system. J Control Release off J Control Release Soc 241:68–80. https://doi.org/10.1016/j.jconrel.2016.09.014
Chen Y, McAndrews KM, Kalluri R (2021) Clinical and therapeutic relevance of cancer-associated fibroblasts. Nat Rev Clin Oncol 18(12):792–804. https://doi.org/10.1038/s41571-021-00546-5
Chen Y, Hu M, Wang S et al (2022) Nano-delivery of salvianolic acid B induces the quiescence of tumor-associated fibroblasts via interfering with TGF-β1/Smad signaling to facilitate chemo- and immunotherapy in desmoplastic tumor. Int J Pharm 623:121953. https://doi.org/10.1016/j.ijpharm.2022.121953
Chen C, Guo Q, Liu Y et al (2023a) Single-cell and spatial transcriptomics reveal POSTN+ cancer-associated fibroblasts correlated with immune suppression and tumour progression in non-small cell lung cancer. Clin Transl Med 13(12):e1515. https://doi.org/10.1002/ctm2.1515
Chen B, Zheng K, Fang S et al (2023b) B7H3 targeting gold nanocage pH-sensitive conjugates for precise and synergistic chemo-photothermal therapy against NSCLC. J Nanobiotechnol 21(1):378. https://doi.org/10.1186/s12951-023-02078-9
Chen Y, Liang Z, Lai M (2024a) Targeting the devil: strategies against cancer-associated fibroblasts in colorectal cancer. Transl Res J Lab Clin Med 270:81–93. https://doi.org/10.1016/j.trsl.2024.04.003
Chen X, Jian D, Xing J et al (2024b) Targeting OGF/OGFR signal to mitigate doxorubicin-induced cardiotoxicity. Free Radic Biol Med 223:398–412. https://doi.org/10.1016/j.freeradbiomed.2024.08.005
Chen M, Xu T, Song L et al (2024c) Nanotechnology based gas delivery system: a "green" strategy for cancer diagnosis and treatment. Theranostics 14(14):5461–5491. https://doi.org/10.7150/thno.98884
Chen X, Ding W, Jiang Y et al (2024d) Emerging strategies for local delivery of immune checkpoint inhibitors to potentiate cancer immunotherapy: current status and future prospects. ACS Appl Mater Interfaces 16(44):59682–59696. https://doi.org/10.1021/acsami.4c12603
Cheng Y, Zou J, He M et al (2024a) Spatiotemporally controlled Pseudomonas exotoxin transgene system combined with multifunctional nanoparticles for breast cancer antimetastatic therapy. J Control Release off J Control Release Soc 367:167–183. https://doi.org/10.1016/j.jconrel.2023.08.011
Cheng Q, Chang Y, Zhang D et al (2024b) Biomineralization synthesis of HoMn nanoparticles for ultrahigh-field-tailored and T1–T2 dual-mode MRI-guided cancer theranostics. ACS Nano 18(41):27853–27868. https://doi.org/10.1021/acsnano.4c00516
Cheng Z, Fobian SF, Gurrieri E et al (2024c) Lipid-based nanosystems: the next generation of cancer immune therapy. J Hematol Oncol 17(1):53. https://doi.org/10.1186/s13045-024-01574-1
Cherukula K, Park MS, Sontyana AG et al (2019) Role of immunosuppressive microenvironment in acquiring immunotolerance post-photothermal therapy. J Korean Med Sci 34(44):e272. https://doi.org/10.3346/jkms.2019.34.e272
Choi Y, Seok SH, Yoon HY, Ryu JH, Kwon IC (2024) Advancing cancer immunotherapy through siRNA-based gene silencing for immune checkpoint blockade. Adv Drug Deliv Rev 209:115306. https://doi.org/10.1016/j.addr.2024.115306
Choueiri TK, Larkin J, Pal S et al (2021) Efficacy and correlative analyses of avelumab plus axitinib versus sunitinib in sarcomatoid renal cell carcinoma: post hoc analysis of a randomized clinical trial. ESMO Open 6(3):100101. https://doi.org/10.1016/j.esmoop.2021.100101

Cirri P, Chiarugi P (2012) Cancer-associated-fibroblasts and tumour cells: a diabolic liaison driving cancer progression. Cancer Metastasis Rev 31(1–2):195–208. https://doi.org/10.1007/s10555-011-9340-x
Cortez E, Roswall P, Pietras K (2014) Functional subsets of mesenchymal cell types in the tumor microenvironment. Semin Cancer Biol 25:3–9. https://doi.org/10.1016/j.semcancer.2013.12.010
Cristofolini T, Dalmina M, Sierra JA et al (2020) Multifunctional hybrid nanoparticles as magnetic delivery systems for siRNA targeting the HER2 gene in breast cancer cells. Mater Sci Eng C Mater Biol Appl 109:110555. https://doi.org/10.1016/j.msec.2019.110555
Cun X, Chen J, Li M et al (2019) Tumor-associated fibroblast-targeted regulation and deep tumor delivery of chemotherapeutic drugs with a multifunctional size-switchable nanoparticle. ACS Appl Mater Interfaces 11(43):39545–39559. https://doi.org/10.1021/acsami.9b13957
D'Aversa E, Salvatori F, Vaccarezza M et al (2024) circRNAs as epigenetic regulators of integrity in blood–brain barrier architecture: mechanisms and therapeutic strategies in multiple sclerosis. Cells 13(16):1316. https://doi.org/10.3390/cells13161316
Dai Q, Wilhelm S, Ding D et al (2018) Quantifying the ligand-coated nanoparticle delivery to cancer cells in solid tumors. ACS Nano 12(8):8423–8435. https://doi.org/10.1021/acsnano.8b03900
Damani M, Jadhav M, Joshi R et al (2024) Advances in gold nanoparticles: synthesis, functionalization strategies, and theranostic applications in cancer. Crit Rev Ther Drug Carrier Syst 41(6):1–56. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2024046712
Dana P, Thumrongsiri N, Tanyapanyachon P, Chonniyom W, Punnakitikashem P, Saengkrit N (2022) Resveratrol loaded liposomes disrupt cancer associated fibroblast communications within the tumor microenvironment to inhibit colorectal cancer aggressiveness. Nanomater Basel Switz 13(1):107. https://doi.org/10.3390/nano13010107
Dasgupta S, Dayagi DY, Haimovich G et al (2023) Global analysis of contact-dependent human-to-mouse intercellular mRNA and lncRNA transfer in cell culture. Elife 12:83584. https://doi.org/10.7554/eLife.83584
de Faria CMG, Bissoli M, Vago R, Spinelli AE, Amendola V (2023) Cytotoxicity of PEG-coated gold and gold-iron alloy nanoparticles: ROS or ferroptosis? Nanomater Basel Switz. 13(23):3044. https://doi.org/10.3390/nano13233044
Deng H, Yang Y, Zuo T et al (2021) Multifunctional ZnO@CuS nanoparticles cluster synergize chemotherapy and photothermal therapy for tumor metastasis. Nanomed Nanotechnol Biol Med 34:102399. https://doi.org/10.1016/j.nano.2021.102399
Dharani S, Cho H, Fernandez JP et al (2024) TALEN-edited allogeneic inducible dual CAR T cells enable effective targeting of solid tumors while mitigating off-tumor toxicity. Mol Ther J Am Soc Gene Ther. 32:3915. https://doi.org/10.1016/j.ymthe.2024.08.018
Donelan W, Dominguez-Gutierrez PR, Kusmartsev S (2022) Deregulated hyaluronan metabolism in the tumor microenvironment drives cancer inflammation and tumor-associated immune suppression. Front Immunol 13:971278. https://doi.org/10.3389/fimmu.2022.971278
Dong L, Li Y, Song X, Sun C, Song X (2024) SFRP1 mediates cancer-associated fibroblasts to suppress cancer cell proliferation and migration in head and neck squamous cell carcinoma. BMC Cancer 24(1):1165. https://doi.org/10.1186/s12885-024-12907-1
Duan H, Liu Y, Gao Z, Huang W (2021) Recent advances in drug delivery systems for targeting cancer stem cells. Acta Pharmaceut Sin B 11:55–70
Duan H, Liu C, Hou Y et al (2022) Sequential delivery of quercetin and paclitaxel for the fibrotic tumor microenvironment remodeling and chemotherapy potentiation via a dual-targeting hybrid micelle-in-liposome system. ACS Appl Mater Interfaces 14(8):10102–10116. https://doi.org/10.1021/acsami.1c23166
Edis Z, Wang J, Waqas MK, Ijaz M, Ijaz M (2021) Nanocarriers-mediated drug delivery systems for anticancer agents: an overview and perspectives. Int J Nanomed 16:1313–1330. https://doi.org/10.2147/IJN.S289443
Eigentler A, Handle F, Schanung S et al (2024) Glucocorticoid treatment influences prostate cancer cell growth and the tumor microenvironment via altered glucocorticoid receptor signaling in prostate fibroblasts. Oncogene 43(4):235–247. https://doi.org/10.1038/s41388-023-02901-5
Eleraky NE, Allam A, Hassan SB, Omar MM (2020) Nanomedicine fight against antibacterial resistance: an overview of the recent pharmaceutical innovations. Pharmaceutics 12(2):142. https://doi.org/10.3390/pharmaceutics12020142
Elewa MAF et al (2024) WRH-2412 alleviates the progression of hepatocellular carcinoma through regulation of TGF-β/β-catenin/α-SMA pathway. J Enzyme Inhib Med Chem 38:2185761
Ernsting MJ, Hoang B, Lohse I et al (2015) Targeting of metastasis-promoting tumor-associated fibroblasts and modulation of pancreatic tumor-associated stroma with a carboxymethylcellulose-docetaxel nanoparticle. J Control Release off J Control Release Soc 206:122–130. https://doi.org/10.1016/j.jconrel.2015.03.023
Esposito M, Yerly L, Shukla P et al (2024) COL10A1 expression distinguishes a subset of cancer-associated fibroblasts present in the stroma of high-risk basal cell carcinoma. Br J Dermatol 191(5):775–790. https://doi.org/10.1093/bjd/ljae258
Faivre S, Santoro A, Kelley RK et al (2019) Novel transforming growth factor beta receptor I kinase inhibitor galunisertib (LY2157299) in advanced hepatocellular carcinoma. Liver Int off J Int Assoc Study Liver 39(8):1468–1477. https://doi.org/10.1111/liv.14113
Fang T, Zhang J, Zuo T et al (2020) Chemo-photothermal combination cancer therapy with ROS scavenging, extracellular matrix depletion, and tumor immune activation by telmisartan and diselenide-paclitaxel prodrug loaded nanoparticles. ACS Appl Mater Interfaces 12(28):31292–31308. https://doi.org/10.1021/acsami.0c10416
Fang Z, Meng Q, Xu J et al (2023) Signaling pathways in cancer-associated fibroblasts: recent advances and future perspectives. Cancer Commun Lond Engl 43(1):3–41. https://doi.org/10.1002/cac2.12392
Feeney OM, Ardipradja K, Noi KF et al (2022) Subcutaneous delivery of a dendrimer-BH3 mimetic improves lymphatic uptake and survival in lymphoma. J Control Release off J Control Release Soc 348:420–430. https://doi.org/10.1016/j.jconrel.2022.05.041
Fei B, Mo Z, Yang J, Wang Z, Li S (2023) Nanodrugs reprogram cancer-associated fibroblasts and normalize tumor vasculatures for sequentially enhancing photodynamic therapy of hepatocellular carcinoma. Int J Nanomed 18:6379–6391. https://doi.org/10.2147/IJN.S429884

Feng L, Luo B, Li B et al (2024) Gold nano frameworks with mesopores for synergistic immune-thermal therapy in hepatic carcinoma: a paradigm shift in immune checkpoint blockade. ACS Appl Mater Interfaces 16(35):45901–45916. https://doi.org/10.1021/acsami.4c06833
Ferraz FS, López JL, Lacerda SMSN et al (2020) Biotechnological approach to induce human fibroblast apoptosis using superparamagnetic iron oxide nanoparticles. J Inorg Biochem 206:111017. https://doi.org/10.1016/j.jinorgbio.2020.111017
Ferrera F, Resaz R, Bari E et al (2024) Silk fibroin nanoparticles for locoregional cancer therapy: preliminary biodistribution in a murine model and microfluidic GMP-like production. Int J Biol Macromol 282:137121. https://doi.org/10.1016/j.ijbiomac.2024.137121
Ferrer-Mayorga G, Gómez-López G, Barbáchano A et al (2017) Vitamin D receptor expression and associated gene signature in tumour stromal fibroblasts predict clinical outcome in colorectal cancer. Gut 66(8):1449–1462. https://doi.org/10.1136/gutjnl-2015-310977
Fitzgerald AA (2024) The role of fibroblast activation protein in health and malignancy. Cancer Metastasis Rev 39:783
Foster DS, Januszyk M, Delitto D et al (2022) Multiomic analysis reveals conservation of cancer-associated fibroblast phenotypes across species and tissue of origin. Cancer Cell 40(11):1392-1406.e7. https://doi.org/10.1016/j.ccell.2022.09.015
Fourniols T, Bastien E, Canevat A, Feron O, Préat V (2020) Inhibition of colorectal cancer-associated fibroblasts by lipid nanocapsules loaded with acriflavine or paclitaxel. Int J Pharm 584:119337. https://doi.org/10.1016/j.ijpharm.2020.119337
Friedman G, Levi-Galibov O, David E et al (2020) Cancer-associated fibroblast compositions change with breast cancer progression linking the ratio of S100A4+ and PDPN+ CAFs to clinical outcome. Nat Cancer 1(7):692–708. https://doi.org/10.1038/s43018-020-0082-y
Fu Y, Saraswat AL, Monpara J, Patel K (2022) Stromal disruption facilitating invasion of a "nano-arsenal" into the solid tumor. Drug Discov Today 27(4):1132–1141. https://doi.org/10.1016/j.drudis.2021.11.015
Gadd DA, Hillary RF, McCartney DL et al (2022) Epigenetic scores for the circulating proteome as tools for disease prediction. Elife 11:e71802. https://doi.org/10.7554/eLife.71802
Gao XJ, Ciura K, Ma Y et al (2024) Toward the integration of machine learning and molecular modeling for designing drug delivery nanocarriers. Adv Mater Deerfield Beach Fla 36(45):e2407793. https://doi.org/10.1002/adma.202407793
Garcia CJG (2022) Stromal HIF2 regulates immune suppression in the pancreatic cancer microenvironmen. Gastroenterology 162:2018
Geng F et al (2019) A DNA vaccine expressing an optimized secreted FAPα induces enhanced anti-tumor activity by altering the tumor microenvironment in a murine model of breast cancer. Vaccine 37:4382
Geng F, Bao X, Dong L et al (2020) Doxorubicin pretreatment enhances FAPα/survivin co-targeting DNA vaccine antitumor activity primarily through decreasing peripheral MDSCs in the 4T1 murine breast cancer model. Oncoimmunology 9(1):1747350. https://doi.org/10.1080/2162402X.2020.1747350
Geng X, Chen H, Zhao L et al (2021) Cancer-associated fibroblast (CAF) heterogeneity and targeting therapy of CAFs in pancreatic cancer. Front Cell Dev Biol 9:655152. https://doi.org/10.3389/fcell.2021.655152
Geng S, Xiang T, Zhang Y et al (2023) Safe engineering of cancer-associated fibroblasts enhances checkpoint blockade immunotherapy. J Control Release off J Control Release Soc 356:272–287. https://doi.org/10.1016/j.jconrel.2023.02.041
Goel M, Mackeyev Y, Krishnan S (2023) Radiolabeled nanomaterial for cancer diagnostics and therapeutics: principles and concepts. Cancer Nanotechnol 14(1):15. https://doi.org/10.1186/s12645-023-00165-y
Gong BS, Wang R, Xu HX, Miao MY, Yao ZZ (2019) Nanotherapy targeting the tumor microenvironment. Curr Cancer Drug Targets 19(7):525–533. https://doi.org/10.2174/1568009619666181220103714
Gong C, Yu X, Zhang W et al (2021) Regulating the immunosuppressive tumor microenvironment to enhance breast cancer immunotherapy using pH-responsive hybrid membrane-coated nanoparticles. J Nanobiotechnol 19(1):58. https://doi.org/10.1186/s12951-021-00805-8
Gong W, Guo Y, Yuan H et al (2023) Loss of exosomal miR-200b-3p from hypoxia cancer-associated fibroblasts promotes tumorigenesis and reduces sensitivity to 5-Flourouracil in colorectal cancer via upregulation of ZEB1 and E2F3. Cancer Gene Ther 30(6):905–916. https://doi.org/10.1038/s41417-023-00591-5
Gong Y, Gao W, Zhang J, Dong X, Zhu D, Ma G (2024) Engineering nanoparticles-enabled tumor-associated macrophages repolarization and phagocytosis restoration for enhanced cancer immunotherapy. J Nanobiotechnol 22(1):341. https://doi.org/10.1186/s12951-024-02622-1
Gorchs L, Ahmed S, Mayer C et al (2020) The vitamin D analogue calcipotriol promotes an anti-tumorigenic phenotype of human pancreatic CAFs but reduces T cell mediated immunity. Sci Rep 10(1):17444. https://doi.org/10.1038/s41598-020-74368-3
Goyal L, Meric-Bernstam F, Hollebecque A et al (2023) Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med 388(3):228–239. https://doi.org/10.1056/NEJMoa2206834
Gu X, Gao Y, Wang P et al (2021) Nano-delivery systems focused on tumor microenvironment regulation and biomimetic strategies for treatment of breast cancer metastasis. J Control Release off J Control Release Soc 333:374–390. https://doi.org/10.1016/j.jconrel.2021.03.039
Gu D, Liu Y, Liu L et al (2024) Mesoporous polydopamine (MPDA)-based drug delivery system for oral chemo-photothermal combinational therapy of orthotopic colon cancer. Int J Biol Macromol 281(Pt 4):136618. https://doi.org/10.1016/j.ijbiomac.2024.136618
Guedes G, Uribe KB, Martínez-Parra L et al (2024) Engineering protein-nanoparticle hybrids as targeted contrast agents. ACS Appl Mater Interfaces 16(44):59849–59861. https://doi.org/10.1021/acsami.4c12799
Guo T, Xu J (2024) Cancer-associated fibroblasts: a versatile mediator in tumor progression, metastasis, and targeted therapy. Cancer Metastasis Rev. https://doi.org/10.1007/s10555-024-10186-7
Guo D, Ji X, Xie H et al (2023) Targeted reprogramming of vitamin B3 metabolism as a nanotherapeutic strategy towards chemoresistant cancers. Adv Mater Deerfield Beach Fla 35(36):e2301257. https://doi.org/10.1002/adma.202301257

Guo SS, Chen MM, Yang YH et al (2024a) Magnetic-vortex nanodonuts enhance ferroptosis effect of tumor ablation through an imaging-guided hyperthermia/radiosensitization strategy. iScience. 27(10):110533. https://doi.org/10.1016/j.isci.2024.110533
Guo Y, Li P, Guo X, Yao C, Yang D (2024b) Synthetic nanoassemblies for regulating organelles: from molecular design to precision therapeutics. ACS Nano 18(44):30224–30246. https://doi.org/10.1021/acsnano.4c10194
Hajialiasgary Najafabadi A, Soheilifar MH, Masoudi-Khoram N (2024) Exosomes in skin photoaging: biological functions and therapeutic opportunity. Cell Commun Signal CCS 22:32. https://doi.org/10.1186/s12964-023-01451-3
Han H, Santos HA (2024) Nano- and micro-platforms in therapeutic proteins delivery for cancer therapy: materials and strategies. Adv Mater Deerfield Beach Fla 36(45):e2409522. https://doi.org/10.1002/adma.202409522
Han C, Liu T, Yin R (2020a) Biomarkers for cancer-associated fibroblasts. Biomark Res 8(1):64. https://doi.org/10.1186/s40364-020-00245-w
Han X, Xu Y, Geranpayehvaghei M, Anderson GJ, Li Y, Nie G (2020b) Emerging nanomedicines for anti-stromal therapy against desmoplastic tumors. Biomaterials 232:119745. https://doi.org/10.1016/j.biomaterials.2019.119745
Han B, Song Y, Park J, Doh J (2022) Nanomaterials to improve cancer immunotherapy based on ex vivo engineered T cells and NK cells. J Control Release off J Control Release Soc 343:379–391. https://doi.org/10.1016/j.jconrel.2022.01.049
Handali S, Moghimipour E, Kouchak M et al (2019) New folate receptor targeted nano liposomes for delivery of 5-fluorouracil to cancer cells: strong implication for enhanced potency and safety. Life Sci 227:39–50. https://doi.org/10.1016/j.lfs.2019.04.030
He Y, Wu S, Rietveld M et al (2024) Application of Doxorubicin-loaded PLGA nanoparticles targeting both tumor cells and cancer-associated fibroblasts on 3D human skin equivalents mimicking melanoma and cutaneous squamous cell carcinoma. Biomater Adv 160:213831. https://doi.org/10.1016/j.bioadv.2024.213831
Helms EJ, Berry MW, Chaw RC et al (2022) Mesenchymal lineage heterogeneity underlies nonredundant functions of pancreatic cancer-associated fibroblasts. Cancer Discov 12(2):484–501. https://doi.org/10.1158/2159-8290.CD-21-0601
Hernández-Jiménez T, Cruz-Nova P, Ancira-Cortez A et al (2022) Toxicity assessment of [(177)Lu]Lu-iFAP/iPSMA nanoparticles prepared under GMP-compliant radiopharmaceutical processes. Nanomater Basel Switz. 12(23):4181. https://doi.org/10.3390/nano12234181
Hong K, Cao J, Jiang W et al (2025) A nanodrug provokes antitumor immune responses via synchronous multicellular regulation for enhanced cancer immunotherapy. J Colloid Interface Sci 678(Pt B):750–762. https://doi.org/10.1016/j.jcis.2024.09.016
Hosseini M, Ahmadi Z, Kefayat A et al (2022) Multifunctional gold helix phototheranostic biohybrid that enables targeted image-guided photothermal therapy in breast cancer. ACS Appl Mater Interfaces 14(33):37447–37465. https://doi.org/10.1021/acsami.2c10028
Hossen MN, Rao G, Dey A, Robertson JD, Bhattacharya R, Mukherjee P (2019) Gold nanoparticle transforms activated cancer-associated fibroblasts to quiescence. ACS Appl Mater Interfaces 11(29):26060–26068. https://doi.org/10.1021/acsami.9b03313
Hou L, Chen D, Hao L et al (2019) Transformable nanoparticles triggered by cancer-associated fibroblasts for improving drug permeability and efficacy in desmoplastic tumors. Nanoscale 11(42):20030–20044. https://doi.org/10.1039/c9nr06438a
Hou L, Chen D, Wang R et al (2021) Transformable honeycomb-like nanoassemblies of carbon dots for regulated multisite delivery and enhanced antitumor chemoimmunotherapy. Angew Chem Int Ed Engl 60(12):6581–6592. https://doi.org/10.1002/anie.202014397
Houthuijzen JM, de Bruijn R, van der Burg E et al (2023) CD26-negative and CD26-positive tissue-resident fibroblasts contribute to functionally distinct CAF subpopulations in breast cancer. Nat Commun 14(1):183. https://doi.org/10.1038/s41467-023-35793-w
Hu JL, Wang W, Lan XL et al (2019) CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial–mesenchymal transition in colorectal cancer. Mol Cancer 18(1):91. https://doi.org/10.1186/s12943-019-1019-x
Hu G, Cheng P, Pan J et al (2020a) An IL6-adenosine positive feedback loop between CD73+ γδTregs and CAFs promotes tumor progression in human breast cancer. Cancer Immunol Res 8(10):1273–1286. https://doi.org/10.1158/2326-6066.CIR-19-0923
Hu Y, Ran M, Wang B, Lin Y, Cheng Y, Zheng S (2020b) Co-delivery of docetaxel and curcumin via nanomicelles for enhancing anti-ovarian cancer treatment. Int J Nanomed 15:9703–9715. https://doi.org/10.2147/IJN.S274083
Hu H, Piotrowska Z, Hare PJ et al (2021) Three subtypes of lung cancer fibroblasts define distinct therapeutic paradigms. Cancer Cell 39(11):1531-1547.e10. https://doi.org/10.1016/j.ccell.2021.09.003
Hu Y, Gao S, Khan AR et al (2022) Tumor microenvironment-responsive size-switchable drug delivery nanosystems. Expert Opin Drug Deliv 19(3):221–234. https://doi.org/10.1080/17425247.2022.2042512
Hu M, Cheng N, Wang S et al (2024a) Salvianolic acid B-loaded polydopamine-modified hollow mesoporous organic silica nanoparticles for treatment of breast cancer metastasis via suppressing cancer-associated fibroblasts. Eur J Pharm Sci off J Eur Fed Pharm Sci 192:106641. https://doi.org/10.1016/j.ejps.2023.106641
Hu Y, Recouvreux MS, Haro M et al (2024b) INHBA (+) cancer-associated fibroblasts generate an immunosuppressive tumor microenvironment in ovarian cancer. NPJ Precis Oncol 8(1):35. https://doi.org/10.1038/s41698-024-00523-y
Huang YK, Busuttil RA, Boussioutas A (2021) The role of innate immune cells in tumor invasion and metastasis. Cancers 13(23):5885. https://doi.org/10.3390/cancers13235885
Huang H, Wang Z, Zhang Y et al (2022a) Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory T cells in pancreatic cancer. Cancer Cell 40(6):656-673.e7. https://doi.org/10.1016/j.ccell.2022.04.011
Huang TX, Tan XY, Huang HS et al (2022b) Targeting cancer-associated fibroblast-secreted WNT2 restores dendritic cell-mediated antitumour immunity. Gut 71(2):333–344. https://doi.org/10.1136/gutjnl-2020-322924
Huang J, Tsang WY, Li ZH, Guan XY (2023) The origin, differentiation, and functions of cancer-associated fibroblasts in gastrointestinal cancer. Cell Mol Gastroenterol Hepatol 16(4):503–511. https://doi.org/10.1016/j.jcmgh.2023.07.001

Huang Y, Wang Y, Zheng T et al (2024a) Development of dual diagnostic-therapeutic nanoformulation effective against pancreatic cancer in animal model. Int J Nanomed 19:9121–9143. https://doi.org/10.2147/IJN.S464788
Huang Q, Ge Y, He Y et al (2024b) The application of nanoparticles targeting cancer-associated fibroblasts. Int J Nanomed 19:3333–3365. https://doi.org/10.2147/IJN.S447350
Huseynov E (2024) Novel nanomaterials for hepatobiliary diseases treatment and future perspectives. Adv Biol Earth Sci. 9(1):81–91. https://doi.org/10.62476/abes9s81
Izci M, Maksoudian C, Gonçalves F et al (2022) Gold nanoparticle delivery to solid tumors: a multiparametric study on particle size and the tumor microenvironment. J Nanobiotechnol 20(1):518. https://doi.org/10.1186/s12951-022-01727-9
Jackson N, Hill I, Alhussan A et al (2023) Dual enhancement in the radiosensitivity of prostate cancer through nanoparticles and chemotherapeutics. Cancer Nanotechnol 14(1):75. https://doi.org/10.1186/s12645-023-00228-0
Jain SM, Nagainallur Ravichandran S, Murali Kumar M et al (2024) Understanding the molecular mechanism responsible for developing therapeutic radiation-induced radioresistance of rectal cancer and improving the clinical outcomes of radiotherapy—a review. Cancer Biol Ther 25(1):2317999. https://doi.org/10.1080/15384047.2024.2317999
Jia M, Zhang D, Zhang C, Li C (2021) Nanoparticle-based delivery systems modulate the tumor microenvironment in pancreatic cancer for enhanced therapy. J Nanobiotechnol 19(1):384. https://doi.org/10.1186/s12951-021-01134-6
Jia X, Li Z, Zhou R et al (2024a) Single cell and bulk RNA sequencing identifies tumor microenvironment subtypes and chemoresistance-related IGF1+ cancer-associated fibroblast in gastric cancer. Biochim Biophys Acta Mol Basis Dis 1870(4):167123. https://doi.org/10.1016/j.bbadis.2024.167123
Jia S, Bode AM, Chen X, Luo X (2024b) Unlocking the potential: targeting metabolic pathways in the tumor microenvironment for cancer therapy. Biochim Biophys Acta Rev Cancer 1879(5):189166. https://doi.org/10.1016/j.bbcan.2024.189166
Jian C, Wu T, Wang L et al (2024) Biomimetic nanoplatform for dual-targeted clearance of activated and senescent cancer-associated fibroblasts to improve radiation resistance in breast cancer. Small Weinh Bergstr Ger 20(25):e2309279. https://doi.org/10.1002/smll.202309279
Jiang M, He K, Qiu T et al (2020) Tumor-targeted delivery of silibinin and IPI-549 synergistically inhibit breast cancer by remodeling the microenvironment. Int J Pharm 581:119239. https://doi.org/10.1016/j.ijpharm.2020.119239
Jotzu C, Alt E, Welte G et al (2010) Adipose tissue-derived stem cells differentiate into carcinoma-associated fibroblast-like cells under the influence of tumor-derived factors. Anal Cell Pathol Amst 33(2):61–79. https://doi.org/10.3233/ACP-CLO-2010-0535
Kahil N, Abouzeinab NS, Hussein MAA, Khalil MI (2024) Intraperitoneal hepatorenal toxicity of zinc oxide and nickel oxide nanoparticles in rats: a systematic review. Nanotoxicology 18:583. https://doi.org/10.1080/17435390.2024.2407352
Kang Y, Li S (2023) Nanomaterials: Breaking through the bottleneck of tumor immunotherapy. Int J Biol Macromol 230:123159. https://doi.org/10.1016/j.ijbiomac.2023.123159
Kaps L, Schuppan D (2020) Targeting cancer associated fibroblasts in liver fibrosis and liver cancer using nanocarriers. Cells 9(9):2027. https://doi.org/10.3390/cells9092027
Kearney JF, Trembath HE, Chan PS et al (2024) Myofibroblastic cancer-associated fibroblast subtype heterogeneity in pancreatic cancer. J Surg Oncol 129(5):860–868. https://doi.org/10.1002/jso.27582
Kerdidani D, Aerakis E, Verrou KM et al (2022) Lung tumor MHCII immunity depends on in situ antigen presentation by fibroblasts. J Exp Med 219(2):e20210815. https://doi.org/10.1084/jem.20210815
Kesharwani P, Halwai K, Jha SK et al (2024) Folate-engineered chitosan nanoparticles: next-generation anticancer nanocarriers. Mol Cancer 23(1):244. https://doi.org/10.1186/s12943-024-02163-z
Kim MG, Shon Y, Kim J, Oh YK (2017) Selective activation of anticancer chemotherapy by cancer-associated fibroblasts in the tumor microenvironment. J Natl Cancer Inst 109(1):djw186. https://doi.org/10.1093/jnci/djw186
Kimiz-Gebologlu I, Oncel SS (2022) Exosomes: large-scale production, isolation, drug loading efficiency, and biodistribution and uptake. J Control Release off J Control Release Soc 347:533–543. https://doi.org/10.1016/j.jconrel.2022.05.027
Kitano Y, Aoki K, Ohka F et al (2021) Urinary MicroRNA-based diagnostic model for central nervous system tumors using nanowire scaffolds. ACS Appl Mater Interfaces 13(15):17316–17329. https://doi.org/10.1021/acsami.1c01754
Kobayashi H, Gieniec KA, Lannagan TRM et al (2022) The origin and contribution of cancer-associated fibroblasts in colorectal carcinogenesis. Gastroenterology 162(3):890–906. https://doi.org/10.1053/j.gastro.2021.11.037
Koumpis E, Papoudou-Bai A, Papathanasiou K, Kolettas E, Kanavaros P, Hatzimichael E (2024) Unraveling the immune microenvironment in diffuse large B-cell lymphoma: prognostic and potential therapeutic implications. Curr Issues Mol Biol 46(7):7048–7064. https://doi.org/10.3390/cimb46070420
Kovács D, Igaz N, Marton A et al (2020) Core-shell nanoparticles suppress metastasis and modify the tumour-supportive activity of cancer-associated fibroblasts. J Nanobiotechnol 18(1):18. https://doi.org/10.1186/s12951-020-0576-x
Krsek A, Jagodic A, Baticic L (2024) Nanomedicine in neuroprotection, neuroregeneration, and blood–rain barrier modulation: a narrative review. Med Kaunas Lith 60(9):1384. https://doi.org/10.3390/medicina60091384
Lai H, Huang R, Weng X, Huang B, Yao J, Pian Y (2024) Classification and applications of nanomaterials in vitro diagnosis. Heliyon 10(11):e32314. https://doi.org/10.1016/j.heliyon.2024.e32314
Lang J, Zhao X, Qi Y et al (2019) Reshaping prostate tumor microenvironment to suppress metastasis via cancer-associated fibroblast inactivation with peptide-assembly-based nanosystem. ACS Nano 13(11):12357–12371. https://doi.org/10.1021/acsnano.9b04857
Laplagne C, Domagala M, Le Naour A et al (2019) Latest advances in targeting the tumor microenvironment for tumor suppression. Int J Mol Sci 20(19):4719. https://doi.org/10.3390/ijms20194719
Lavie D, Ben-Shmuel A, Erez N, Scherz-Shouval R (2022) Cancer-associated fibroblasts in the single-cell era. Nat Cancer 3(7):793–807. https://doi.org/10.1038/s43018-022-00411-z
Lee YE. Synergistic therapeutic combination with a CAF inhibitor enhances CAR-NK-mediated cytotoxicity via reduction of CAF-released IL-6. J Immunothera Cancer. 2023.

Lee KJ, Lee YM, Yang SB et al (2024) A novel chemically engineered multifunctional statin conjugate as self-assembled nanoparticles inhibiting bile acid transporters. J Control Release off J Control Release Soc 372:885–900. https://doi.org/10.1016/j.jconrel.2024.07.008
Leong TKM, Lo WS, Lee WEZ et al (2021) Leveraging advances in immunopathology and artificial intelligence to analyze in vitro tumor models in composition and space. Adv Drug Deliv Rev 177:113959. https://doi.org/10.1016/j.addr.2021.113959
Li W, Zhang X, Wang J et al (2017) TGFβ1 in fibroblasts-derived exosomes promotes epithelial–mesenchymal transition of ovarian cancer cells. Oncotarget 8(56):96035–96047. https://doi.org/10.18632/oncotarget.21635
Li L, Zhou S, Lv N et al (2018a) Photosensitizer-encapsulated ferritins mediate photodynamic therapy against cancer-associated fibroblasts and improve tumor accumulation of nanoparticles. Mol Pharm 15(8):3595–3599. https://doi.org/10.1021/acs.molpharmaceut.8b00419
Li M, Zhang F, Su Y, Zhou J, Wang W (2018b) Nanoparticles designed to regulate tumor microenvironment for cancer therapy. Life Sci 201:37–44. https://doi.org/10.1016/j.lfs.2018.03.044
Li B, Pei G, Yao J, Ding Q, Jia P, Zhao Z (2021a) Cell-type deconvolution analysis identifies cancer-associated myofibroblast component as a poor prognostic factor in multiple cancer types. Oncogene 40(28):4686–4694. https://doi.org/10.1038/s41388-021-01870-x
Li Z, Sun C, Qin Z (2021b) Metabolic reprogramming of cancer-associated fibroblasts and its effect on cancer cell reprogramming. Theranostics 11(17):8322–8336. https://doi.org/10.7150/thno.62378
Li Z, Liu C, Li C et al (2021c) Irinotecan/scFv co-loaded liposomes coaction on tumor cells and CAFs for enhanced colorectal cancer therapy. J Nanobiotechnol 19(1):421. https://doi.org/10.1186/s12951-021-01172-0
Li X, Zhou J, Wang X et al (2023) Pancreatic cancer and fibrosis: targeting metabolic reprogramming and crosstalk of cancer-associated fibroblasts in the tumor microenvironment. Front Immunol 14:1152312. https://doi.org/10.3389/fimmu.2023.1152312
Li D, Cao D, Sun Y et al (2024a) The roles of epigallocatechin gallate in the tumor microenvironment, metabolic reprogramming, and immunotherapy. Front Immunol 15:1331641. https://doi.org/10.3389/fimmu.2024.1331641
Li Z, Zhu Y, Zhang Z et al (2024b) Softness-aided mild hyperthermia boosts stiff nanomedicine by regulating tumor mechanics. Adv Sci Weinh Baden-Wurtt Ger 11(26):e2306730. https://doi.org/10.1002/advs.202306730
Li Y, Tazawa H, Nagai Y et al (2024c) senescent fibroblasts potentiate peritoneal metastasis of diffuse-type gastric cancer cells via IL-8-mediated crosstalk. Anticancer Res 44(6):2497–2509. https://doi.org/10.21873/anticanres.17056
Li C, Guo H, Zhai P et al (2024d) Spatial and single-cell transcriptomics reveal a cancer-associated fibroblast subset in HNSCC that restricts infiltration and antitumor activity of CD8+ T cells. Cancer Res 84(2):258–275. https://doi.org/10.1158/0008-5472.CAN-23-1448
Li C, Wang Z, Zhang Y et al (2024e) Efficient sequential co-delivery nanosystem for inhibition of tumor and tumor-associated fibroblast-induced resistance and metastasis. Int J Nanomed 19:1749–1766. https://doi.org/10.2147/IJN.S427783
Li X, Sun X, Wang Y, Chen H, Gao Y (2025) A nanotheranostics with hypoxia-switchable fluorescence and photothermal effect for hypoxia imaging-guided immunosuppressive tumor microenvironment modulation. J Colloid Interface Sci 678(Pt C):897–912. https://doi.org/10.1016/j.jcis.2024.09.133
Liang Q, Zhou L, Li Y, Liu J, Liu Y (2022) Nano drug delivery system reconstruct tumour vasculature for the tumour vascular normalisation. J Drug Target 30(2):119–130. https://doi.org/10.1080/1061186X.2021.1927056
Liang W, Zhang W, Tian J et al (2024a) Advances in carbohydrate-based nanoparticles for targeted therapy of inflammatory bowel diseases: a review. Int J Biol Macromol 281(Pt 4):136392. https://doi.org/10.1016/j.ijbiomac.2024.136392
Liang J, Ji F, Abdullah ALB et al (2024b) Micro/nano-plastics impacts in cardiovascular systems across species. Sci Total Environ 942:173770. https://doi.org/10.1016/j.scitotenv.2024.173770
Liu L, Zhao X (2024) Preparation of environmentally responsive PDA&DOX@LAC live drug carrier for synergistic tumor therapy. Sci Rep 14(1):15927. https://doi.org/10.1038/s41598-024-66966-2
Liu Q, Chen F, Hou L et al (2018) Nanocarrier-mediated chemo-immunotherapy arrested cancer progression and induced tumor dormancy in desmoplastic melanoma. ACS Nano 12(8):7812–7825. https://doi.org/10.1021/acsnano.8b01890
Liu M, Song W, Huang L (2019a) Drug delivery systems targeting tumor-associated fibroblasts for cancer immunotherapy. Cancer Lett 448:31–39. https://doi.org/10.1016/j.canlet.2019.01.032
Liu T, Han C, Wang S et al (2019b) Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. J Hematol OncolJ Hematol Oncol 12(1):86. https://doi.org/10.1186/s13045-019-0770-1
Liu C, Chiang B, Lewin Mejia D, Luker KE, Luker GD, Lee A (2019c) Mammary fibroblasts remodel fibrillar collagen microstructure in a biomimetic nanocomposite hydrogel. Acta Biomater 83:221–232. https://doi.org/10.1016/j.actbio.2018.11.010
Liu J, Ren L, Li S et al (2021) The biology, function, and applications of exosomes in cancer. Acta Pharm Sin B. 11(9):2783. https://doi.org/10.1016/j.apsb.2021.01.001
Liu Y, Ye Z, Yang W et al (2022a) A triple enhanced permeable gold nanoraspberry designed for positive feedback interventional therapy. J Control Release off J Control Release Soc 345:120–137. https://doi.org/10.1016/j.jconrel.2022.03.010
Liu Q, Wang X, Liao YP et al (2022b) Use of a liver-targeting nanoparticle platform to intervene in peanut-induced anaphylaxis through delivery of an Ara h2 T-cell epitope. Nano Today 42:101370. https://doi.org/10.1016/j.nantod.2021.101370
Liu J, Wang Y, Mu C et al (2022c) Pancreatic tumor eradication via selective Pin1 inhibition in cancer-associated fibroblasts and T lymphocytes engagement. Nat Commun 13(1):4308. https://doi.org/10.1038/s41467-022-31928-7
Liu Y, Cheng W, Xin H et al (2023a) Nanoparticles advanced from preclinical studies to clinical trials for lung cancer therapy. Cancer Nanotechnol 14(1):28. https://doi.org/10.1186/s12645-023-00174-x

Liu Y, Sun Y, Wang P et al (2023b) FAP-targeted CAR-T suppresses MDSCs recruitment to improve the antitumor efficacy of claudin18.2-targeted CAR-T against pancreatic cancer. J Transl Med 21(1):255. https://doi.org/10.1186/s12967-023-04080-z
Liu W, Song X, Jiang Q et al (2024a) Transition metal oxide nanomaterials: new weapons to boost anti-tumor immunity cycle. Nanomater Basel Switz 14(13):1064. https://doi.org/10.3390/nano14131064
Liu L, Zhang B, Wu X et al (2024b) Bioresponsive nanocomplex integrating cancer-associated fibroblast deactivation and immunogenic chemotherapy for rebuilding immune-excluded tumors. Nanomed Nanotechnol Biol Med 58:102743. https://doi.org/10.1016/j.nano.2024.102743
Liu Z, Zhang Z, Zhang Y et al (2024c) Spatial transcriptomics reveals that metabolic characteristics define the tumor immunosuppression microenvironment via iCAF transformation in oral squamous cell carcinoma. Int J Oral Sci 16(1):9. https://doi.org/10.1038/s41368-023-00267-8
Liu H, Lu Y, Zong J et al (2024d) Engineering dendritic cell biomimetic membrane as a delivery system for tumor targeted therapy. J Nanobiotechnol 22(1):663. https://doi.org/10.1186/s12951-024-02913-7
Lo YL, Li CY, Chou TF et al (2024) Exploring in vivo combinatorial chemo-immunotherapy: addressing p97 suppression and immune reinvigoration in pancreatic cancer with tumor microenvironment-responsive nanoformulation. Biomed Pharmacother Biomed Pharmacother 175:116660. https://doi.org/10.1016/j.biopha.2024.116660
Lu L, Gao Y, Huang D et al (2023) Targeting integrin α5 in fibroblasts potentiates colorectal cancer response to PD-L1 blockade by affecting extracellular-matrix deposition. J Immunother Cancer 11(12):e007447. https://doi.org/10.1136/jitc-2023-007447
Lu Q, Kou D, Lou S et al (2024) Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. J Hematol OncolJ Hematol Oncol 17:16. https://doi.org/10.1186/s13045-024-01535-8
Luo H, Xia X, Huang LB et al (2022) Pan-cancer single-cell analysis reveals the heterogeneity and plasticity of cancer-associated fibroblasts in the tumor microenvironment. Nat Commun 13(1):6619. https://doi.org/10.1038/s41467-022-34395-2
Luo M, Zhao FK, Wang YM, Bian J (2024a) Au@Pd nanozyme-mediated catalytic therapy: a novel strategy for targeting tumor microenvironment in cancer treatment. J Transl Med 22(1):814. https://doi.org/10.1186/s12967-024-05631-8
Luo M, Wang YM, Zhao FK, Luo Y. Recent advances in nanomaterial-mediated cell death for cancer therapy. Adv Healthc Mater. 2024:e2402697. https://doi.org/10.1002/adhm.202402697.
Ma G, Severic M, Barker M et al (2021) Dually targeted bioinspired nanovesicle delays advanced prostate cancer tumour growth in vivo. Acta Biomater 134:559–575. https://doi.org/10.1016/j.actbio.2021.07.021
Macy AM, Herrmann LM, Adams AC, Hastings KT (2023) Major histocompatibility complex class II in the tumor microenvironment: functions of nonprofessional antigen-presenting cells. Curr Opin Immunol 83:102330. https://doi.org/10.1016/j.coi.2023.102330
Mahajan K, Bhattacharya S (2024) The advancement and obstacles in improving the stability of nanocarriers for precision drug delivery in the field of nanomedicine. Curr Top Med Chem 24(8):686–721. https://doi.org/10.2174/0115680266287101240214071718
Maia A, Wiemann S (2021) Cancer-associated fibroblasts: implications for cancer therapy. Cancers 13(14):3526. https://doi.org/10.3390/cancers13143526
Mao X, Xu J, Wang W et al (2021) Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. Mol Cancer 20(1):131. https://doi.org/10.1186/s12943-021-01428-1
Mardhian DF, Storm G, Bansal R, Prakash J (2018) Nano-targeted relaxin impairs fibrosis and tumor growth in pancreatic cancer and improves the efficacy of gemcitabine in vivo. J Control Release off J Control Release Soc 290:1–10. https://doi.org/10.1016/j.jconrel.2018.09.031
Mardhian DF, Vrynas A, Storm G, Bansal R, Prakash J (2020) FGF2 engineered SPIONs attenuate tumor stroma and potentiate the effect of chemotherapy in 3D heterospheroidal model of pancreatic tumor. Nanotheranostics 4(1):26–39. https://doi.org/10.7150/ntno.38092
Marwedel B, De May H, Anderson L, et al. TLR agonist nano immune therapy clears peritoneal and systemic ovarian cancer. Adv Healthc Mater. 2024:e2402966. https://doi.org/10.1002/adhm.202402966.
Matsui T et al (1989) Isolation of a novel receptor cDNA establishes the existence of two PDGF receptor genes. Science 234:800
Mauro N, Scialabba C, Pitarresi G, Giammona G (2017) Enhanced adhesion and in situ photothermal ablation of cancer cells in surface-functionalized electrospun microfiber scaffold with graphene oxide. Int J Pharm 526(1–2):167–177. https://doi.org/10.1016/j.ijpharm.2017.04.045
Melchionna R, Trono P, Di Carlo A, Di Modugno F, Nisticò P (2023) Transcription factors in fibroblast plasticity and CAF heterogeneity. J Exp Clin Cancer Res CR 42(1):347. https://doi.org/10.1186/s13046-023-02934-4
Melissari MT, Chalkidi N, Sarris ME, Koliaraki V (2020) Fibroblast reprogramming in gastrointestinal cancer. Front Cell Dev Biol 8:630. https://doi.org/10.3389/fcell.2020.00630
Meng X, Zhu G, Yang YG, Sun T (2024) Targeted delivery strategies: the interactions and applications of nanoparticles in liver diseases. Biomed Pharmacother Biomed Pharmacother 175:116702. https://doi.org/10.1016/j.biopha.2024.116702
Mirza-Aghazadeh-Attari M, Mihanfar A, Yousefi B, Majidinia M (2022) Nanotechnology-based advances in the efficient delivery of melatonin. Cancer Cell Int 22(1):43. https://doi.org/10.1186/s12935-022-02472-7
Montazersaheb S et al (2024) Green-synthesized silver nanoparticles from peel extract of pumpkin as a potent radiosensitizer against triple-negative breast cancer (TNBC). Cancer Nanotechnol. https://doi.org/10.1186/s12645-024-00285-z
Monteran L, Erez N (2019) The dark side of fibroblasts: cancer-associated fibroblasts as mediators of immunosuppression in the tumor microenvironment. Front Immunol 10:1835. https://doi.org/10.3389/fimmu.2019.01835
Morgan A, Griffin M, Kameni L, Wan DC, Longaker MT, Norton JA (2023) Medical biology of cancer-associated fibroblasts in pancreatic cancer. Biology 12(8):1044. https://doi.org/10.3390/biology12081044

Mu J, Gao S, Yang J, Wu F, Zhou H (2021) Fundamental and clinical applications of materials based on cancer-associated fibroblasts in cancers. Int J Mol Sci 22(21):11671. https://doi.org/10.3390/ijms222111671
Mu Y, Zhang Z, Zhou H, Ma L, Wang DA (2024) Applications of nanotechnology in remodeling the tumour microenvironment for glioblastoma treatment. Biomater Sci 12(16):4045–4064. https://doi.org/10.1039/d4bm00665h
Muchlińska A et al (2022) Alpha-smooth muscle actin-positive cancer-associated fibroblasts secreting osteopontin promote growth of luminal breast cancer. Cell Mol Biol Lett 27:45
Naseer F, Ahmed M, Majid A, Kamal W, Phull AR (2022) Green nanoparticles as multifunctional nanomedicines: insights into anti-inflammatory effects, growth signaling and apoptosis mechanism in cancer. Semin Cancer Biol 86(Pt 2):310–324. https://doi.org/10.1016/j.semcancer.2022.06.014
Nicolás-Boluda A, Vaquero J, Laurent G et al (2020) Photothermal depletion of cancer-associated fibroblasts normalizes tumor stiffness in desmoplastic cholangiocarcinoma. ACS Nano 14(5):5738–5753. https://doi.org/10.1021/acsnano.0c00417
Norton J, Foster D, Chinta M, Titan A, Longaker M (2020) Pancreatic cancer associated fibroblasts (CAF): under-explored target for pancreatic cancer treatment. Cancers 12(5):1347. https://doi.org/10.3390/cancers12051347
Noureddine A, Marwedel B, Tang L, Medina LY, Serda RE (2023) Specific tumor localization of immunogenic lipid-coated mesoporous silica nanoparticles following intraperitoneal administration in a mouse model of serous epithelial ovarian cancer. Cancers 15(18):4626. https://doi.org/10.3390/cancers15184626
Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E (2020) In search of definitions: cancer-associated fibroblasts and their markers. Int J Cancer 146(4):895–905. https://doi.org/10.1002/ijc.32193
Orlowski P, Tomaszewska E, Ranoszek-Soliwoda K et al (2018) Tannic acid-modified silver and gold nanoparticles as novel stimulators of dendritic cells activation. Front Immunol 9:1115. https://doi.org/10.3389/fimmu.2018.01115
Ou L, Wang H, Huang H et al (2022) Preclinical platforms to study therapeutic efficacy of human γδ T cells. Clin Transl Med 12(6):e814. https://doi.org/10.1002/ctm2.814
Overchuk M, Weersink RA, Wilson BC, Zheng G (2023) Photodynamic and photothermal therapies: synergy opportunities for nanomedicine. ACS Nano 17(9):7979–8003. https://doi.org/10.1021/acsnano.3c00891
Owen JS, Clayton A, Pearson HB (2022) Cancer-associated fibroblast heterogeneity, activation and function: implications for prostate cancer. Biomolecules 13(1):67. https://doi.org/10.3390/biom13010067
Palombarini F, Masciarelli S, Incocciati A et al (2021) Self-assembling ferritin-dendrimer nanoparticles for targeted delivery of nucleic acids to myeloid leukemia cells. J Nanobiotechnol 19(1):172. https://doi.org/10.1186/s12951-021-00921-5
Pan S, Yin R, Zhu H, Shen S, Li Z, Liu B (2024) Prostate cancer cancer-associated fibroblasts with stable markers post-androgen deprivation therapy associated with tumor progression and castration resistant prostate cancer. Cancer Sci 115(9):2893–2907. https://doi.org/10.1111/cas.16267
Park D, Sahai E, Rullan A (2020) SnapShot: cancer-associated fibroblasts. Cell 181(2):486-486.e1. https://doi.org/10.1016/j.cell.2020.03.013
Pedersen C, Chen VT, Herbst P et al (2024) Target specification and therapeutic potential of extracellular vesicles for regulating corneal angiogenesis, lymphangiogenesis, and nerve repair. Ocul Surf. https://doi.org/10.1016/j.jtos.2024.10.005
Pednekar K, Minnee J, de Vries IJM, Prakash J (2024) Targeted nanomedicine for reprogramming the tumor innate immune system: from bench to bedside. Eur J Pharm Biopharm off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV 204:114510. https://doi.org/10.1016/j.ejpb.2024.114510
Pei Y, Chen L, Huang Y et al (2019) Sequential targeting TGF-β signaling and KRAS mutation increases therapeutic efficacy in pancreatic cancer. Small Weinh Bergstr Ger 15(24):e1900631. https://doi.org/10.1002/smll.201900631
Peng C, Xu Y, Wu J, Wu D, Zhou L, Xia X (2024) TME-related biomimetic strategies against cancer. Int J Nanomed 19:109–135. https://doi.org/10.2147/IJN.S441135
Perez-Penco M, LaradelaTorre L, Lecoq I, Martinenaite E, Andersen MH (2024) TGFβ-specific T cells induced by a TGFβ-derived immune modulatory vaccine both directly and indirectly modulate the phenotype of tumor-associated macrophages and fibroblasts. J Immunother Cancer 12(2):e008405. https://doi.org/10.1136/jitc-2023-008405
Picard FSR, Lutz V, Brichkina A et al (2023) IL-17A-producing CD8+ T cells promote PDAC via induction of inflammatory cancer-associated fibroblasts. Gut 72(8):1510–1522. https://doi.org/10.1136/gutjnl-2022-327855
Piersma B, Hayward MK, Weaver VM (2020) Fibrosis and cancer: a strained relationship. Biochim Biophys Acta Rev Cancer 1873(2):188356. https://doi.org/10.1016/j.bbcan.2020.188356
Pietrobono S, Sabbadini F, Bertolini M et al (2024) Autotaxin secretion is a stromal mechanism of adaptive resistance to TGFβ inhibition in pancreatic ductal adenocarcinoma. Cancer Res 84(1):118–132. https://doi.org/10.1158/0008-5472.CAN-23-0104
Ping Q, Yan R, Cheng X et al (2021) Cancer-associated fibroblasts: overview, progress, challenges, and directions. Cancer Gene Ther 28(9):984–999. https://doi.org/10.1038/s41417-021-00318-4
Piwocka O, Piotrowski I, Suchorska WM, Kulcenty K (2024) Dynamic interactions in the tumor niche: how the cross-talk between CAFs and the tumor microenvironment impacts resistance to therapy. Front Mol Biosci 11:1343523. https://doi.org/10.3389/fmolb.2024.1343523
Pradhan R, Paul S, Das B et al (2023) Resveratrol nanoparticle attenuates metastasis and angiogenesis by deregulating inflammatory cytokines through inhibition of CAFs in oral cancer by CXCL-12/IL-6-dependent pathway. J Nutr Biochem 113:109257. https://doi.org/10.1016/j.jnutbio.2022.109257
Pradip D, Jennifer A, Nandini D (2021) Cancer-associated fibroblasts in conversation with tumor cells in endometrial cancers: a partner in crime. Int J Mol Sci 22(17):9121. https://doi.org/10.3390/ijms22179121
Priwitaningrum DL, Blondé JBG, Sridhar A et al (2016) Tumor stroma-containing 3D spheroid arrays: a tool to study nanoparticle penetration. J Control Release off J Control Release Soc 244(Pt B):257–268. https://doi.org/10.1016/j.jconrel.2016.09.004
Qin H, Ding Y, Mujeeb A, Zhao Y, Nie G (2017) Tumor microenvironment targeting and responsive peptide-based nanoformulations for improved tumor therapy. Mol Pharmacol 92(3):219–231. https://doi.org/10.1124/mol.116.108084

Qin Y, Zu X, Li Y et al (2023) A cancer-associated fibroblast subtypes-based signature enables the evaluation of immunotherapy response and prognosis in bladder cancer. iScience. 26(9):107722. https://doi.org/10.1016/j.isci.2023.107722
Qiu X, Li Z, Han X et al (2019) Tumor-derived nanovesicles promote lung distribution of the therapeutic nanovector through repression of Kupffer cell-mediated phagocytosis. Theranostics 9(9):2618–2636. https://doi.org/10.7150/thno.32363
Qiu N, Lv QY, Li CL et al (2024) Optimization and mechanisms of proteolytic enzyme immobilization onto large-pore mesoporous silica nanoparticles: enhanced tumor penetration. Int J Biol Macromol 271(Pt 1):132626. https://doi.org/10.1016/j.ijbiomac.2024.132626
Ramesh K, Truong A, Wang Y, Rusckowski M, Gkikas M (2022) Ligand-specific nano-contrast agents promote enhanced breast cancer CT detection at 0.5 mg Au. Int J Mol Sci 23(17):9926. https://doi.org/10.3390/ijms23179926
Ran Q, Chen L (2024) Eniluracil blocks AREG signalling-induced pro-inflammatory fibroblasts of melanoma in heart failure. ESC Heart Fail. https://doi.org/10.1002/ehf2.15110
Ren L, Wang Y, Tang Y et al (2024) US/PA/MR multimodal imaging-guided multifunctional genetically engineered bio-targeted synergistic agent for tumor therapy. J Nanobiotechnol 22(1):615. https://doi.org/10.1186/s12951-024-02868-9
Rimal R, Desai P, Daware R et al (2022) Cancer-associated fibroblasts: origin, function, imaging, and therapeutic targeting. Adv Drug Deliv Rev 189:114504. https://doi.org/10.1016/j.addr.2022.114504
Rizzolio S, Giordano S, Corso S (2022) The importance of being CAFs (in cancer resistance to targeted therapies). J Exp Clin Cancer Res CR 41(1):319. https://doi.org/10.1186/s13046-022-02524-w
Rodponthukwaji K, Thongchot S, Deureh S et al (2024) Development of cancer-associated fibroblasts-targeting polymeric nanoparticles loaded with 8-*O*-methylfusarubin for breast cancer treatment. Int J Pharm x 8:100294. https://doi.org/10.1016/j.ijpx.2024.100294
Rosic G (2024) Cancer signaling, cell/gene therapy, diagnosis and role of nanobiomaterials. Adv Biol Earth Sci. 9(Special Issue):11–34. https://doi.org/10.62476/abes9s11
Roy Chaudhuri T, Straubinger NL, Pitoniak RF et al (2016) Tumor-priming smoothened inhibitor enhances deposition and efficacy of cytotoxic nanoparticles in a pancreatic cancer model. Mol Cancer Ther 15(1):84–93. https://doi.org/10.1158/1535-7163.MCT-15-0602
Ruan S et al (2022) Acidic and hypoxic tumor microenvironment regulation by CaO_2-loaded polydopamine nanoparticles. J Nanobiotechnol 20:544
Sahai E, Astsaturov I, Cukierman E et al (2020) A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer 20(3):174–186. https://doi.org/10.1038/s41568-019-0238-1
Salotto KE, Olson WC, Pollack KE et al (2022) A nano-enhanced vaccine for metastatic melanoma immunotherapy. Cancer Drug Resist Alhambra Calif 5(3):829–845. https://doi.org/10.20517/cdr.2021.132
Santi A, Kugeratski FG, Zanivan S (2018) Cancer associated fibroblasts: the architects of stroma remodeling. Proteomics 18(5–6):e1700167. https://doi.org/10.1002/pmic.201700167
Santolla MF, Talia M, Maggiolini M (2021) S100A4 is involved in stimulatory effects elicited by the FGF2/FGFR1 signaling pathway in triple-negative breast cancer (TNBC) cells. Int J Mol Sci 22(9):4720. https://doi.org/10.3390/ijms22094720
Santos-Coquillat A, Herreros-Pérez D, Samaniego R et al (2022) Dual-labeled nanoparticles based on small extracellular vesicles for tumor detection. Biol Direct 17(1):31. https://doi.org/10.1186/s13062-022-00345-7
Schütz S, Solé-Boldo L, Lucena-Porcel C et al (2023) Functionally distinct cancer-associated fibroblast subpopulations establish a tumor promoting environment in squamous cell carcinoma. Nat Commun 14(1):5413. https://doi.org/10.1038/s41467-023-41141-9
Seo J, Do Yoo J, Kim M et al (2021) Fibrinolytic nanocages dissolve clots in the tumor microenvironment, improving the distribution and therapeutic efficacy of anticancer drugs. Exp Mol Med 53(10):1592–1601. https://doi.org/10.1038/s12276-021-00688-7
Sharbeen G, McCarroll JA, Akerman A et al (2021) Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma determine response to SLC7A11 inhibition. Cancer Res 81(13):3461–3479. https://doi.org/10.1158/0008-5472.CAN-20-2496
Sharma M, Turaga RC, Yuan Y et al (2021) Simultaneously targeting cancer-associated fibroblasts and angiogenic vessel as a treatment for TNBC. J Exp Med 218(4):e20200712. https://doi.org/10.1084/jem.20200712
Shen W, Yao PA, Li W et al (2023) Cancer-associated fibroblast-targeted nanodrugs reshape colorectal tumor microenvironments to suppress tumor proliferation, metastasis and improve drug penetration. J Mater Chem B 11(9):1871–1880. https://doi.org/10.1039/d2tb02253b
Shi W, Liu Y, Qiu X, Yang L, Lin G (2023) Cancer-associated fibroblasts-derived exosome-mediated transfer of miR-345-5p promotes the progression of colorectal cancer by targeting CDKN1A. Carcinogenesis 44(4):317–327. https://doi.org/10.1093/carcin/bgad014
Shinde AV, Humeres C, Frangogiannis NG (2017) The role of α-smooth muscle actin in fibroblast-mediated matrix contraction and remodeling. Biochim Biophys Acta BBA Mol Basis Disease 1863:298
Simon T, Salhia B (2022) Cancer-associated fibroblast subpopulations with diverse and dynamic roles in the tumor microenvironment. Mol Cancer Res MCR 20(2):183–192. https://doi.org/10.1158/1541-7786.MCR-21-0282
Singh AV, Bhardwaj P, Upadhyay AK et al (2024a) Navigating regulatory challenges in molecularly tailored nanomedicine. Explor BioMat-x 1(2):124–134. https://doi.org/10.37349/ebmx.2024.00009
Singh AV, Chandrasekar V, Prabhu VM et al (2024b) Sustainable bioinspired materials for regenerative medicine: balancing toxicology, environmental impact, and ethical considerations. Biomed Mater Bristol Engl. 19(6):060501. https://doi.org/10.1088/1748-605X/ad85bb
Sitia L, Bonizzi A, Mazzucchelli S et al (2021) Selective targeting of cancer-associated fibroblasts by engineered H-ferritin nanocages loaded with navitoclax. Cells 10(2):328. https://doi.org/10.3390/cells10020328
Sohn EJ (2020) MiRNA 3613-5p and MiRNA 3916 rescued the inhibition of cell migration in CNOT2 depleted MDA-MD-231 cells. Transl Cancer Res 9(8):4542–4549. https://doi.org/10.21037/tcr-19-2821

Song Z, Deng X, Jiang L et al (2024) Copper-consuming nanoplatform for alleviating hypoxia and overcoming resistance to sonodynamic therapy of breast cancer. ACS Appl Mater Interfaces 16(43):58357–58369. https://doi.org/10.1021/acsami.4c13687
Spandau DF, Chen R, Wargo JJ et al (2021) Randomized controlled trial of fractionated laser resurfacing on aged skin as prophylaxis against actinic neoplasia. J Clin Invest 131(19):e150972. https://doi.org/10.1172/JCI150972
Srivastava P, Rütter M, Antoniraj G, Ventura Y, David A (2024) dendritic cell-targeted nanoparticles enhance T cell activation and antitumor immune responses by boosting antigen presentation and blocking PD-L1 pathways. ACS Appl Mater Interfaces 16(40):53577–53590. https://doi.org/10.1021/acsami.4c12821
Su MC, Nethi SK, Dhanyamraju PK, Prabha S (2023) Nanomedicine strategies for targeting tumor stroma. Cancers 15(16):4145. https://doi.org/10.3390/cancers15164145
Suh J, Kim DH, Lee YH, Jang JH, Surh YJ (2020) Fibroblast growth factor-2, derived from cancer-associated fibroblasts, stimulates growth and progression of human breast cancer cells via FGFR1 signaling. Mol Carcinog 59(9):1028–1040. https://doi.org/10.1002/mc.23233
Sui M, Wang C, Tian Y, Zhang H (2024) Laser-enzyme dual responsive liposomes to regulate autophagy in synergy with phototherapy for melanoma treatment. J Drug Target 32:1305. https://doi.org/10.1080/1061186X.2024.2386624
Sun S, Zhang Y, Li Y, Wei L (2023) Crosstalk between colorectal cancer cells and cancer-associated fibroblasts in the tumor microenvironment mediated by exosomal noncoding RNAs. Front Immunol 14:1161628. https://doi.org/10.3389/fimmu.2023.1161628
Sun L, Ke M, Yin M et al (2024a) Extracellular vesicle-encapsulated microRNA-296-3p from cancer-associated fibroblasts promotes ovarian cancer development through regulation of the PTEN/AKT and SOCS6/STAT3 pathways. Cancer Sci 115(1):155–169. https://doi.org/10.1111/cas.16014
Sun W, Xie S, Liu SF, Hu X, Xing D (2024b) Evolving tumor characteristics and smart nanodrugs for tumor immunotherapy. Int J Nanomed 19:3919–3942. https://doi.org/10.2147/IJN.S453265
Sun X, Wu Y, Wang X et al (2024c) Beyond small molecules: antibodies and peptides for fibroblast activation protein targeting radiopharmaceuticals. Pharmaceutics 16(3):345. https://doi.org/10.3390/pharmaceutics16030345
Sun X, Li Y, Liu X, Cui D, Shi Y, Huang G (2024d) Tumor-specific enhanced NIR-II photoacoustic imaging via photothermal and low-pH coactivated AuNR@PNIPAM-VAA nanogel. J Nanobiotechnol 22(1):326. https://doi.org/10.1186/s12951-024-02617-y
Sung JY, Lee JW (2024) Cancer-associated fibroblast subtypes reveal distinct gene signatures in the tumor immune microenvironment of vestibular schwannoma. Cells 13(19):1669. https://doi.org/10.3390/cells13191669
Tagaras N, Song H, Sahar S, Tong W, Mao Z, Buerki-Thurnherr T (2024) Safety landscape of therapeutic nanozymes and future research directions. Adv Sci Weinh Baden-Wurtt Ger. 11:e2407816. https://doi.org/10.1002/advs.202407816
Tan YN, Li YP, Huang JD et al (2021) Thermal-sensitive lipid nanoparticles potentiate anti-PD therapy through enhancing drug penetration and T lymphocytes infiltration in metastatic tumor. Cancer Lett 522:238–254. https://doi.org/10.1016/j.canlet.2021.09.031
Tan YN, Huang JD, Li YP et al (2022) Near-infrared responsive membrane nanovesicles amplify homologous targeting delivery of anti-PD immunotherapy against metastatic tumors. Adv Healthc Mater 11(6):e2101496. https://doi.org/10.1002/adhm.202101496
Tang L, Mei Y, Shen Y et al (2021) Nanoparticle-mediated targeted drug delivery to remodel tumor microenvironment for cancer therapy. Int J Nanomed 16:5811–5829. https://doi.org/10.2147/IJN.S321416
Tang PCT, Chung JYF, Xue VWW et al (2022) Smad3 promotes cancer-associated fibroblasts generation via macrophage-myofibroblast transition. Adv Sci Weinh Baden-Wurtt Ger 9(1):e2101235. https://doi.org/10.1002/advs.202101235
Tarbit E, Singh I, Peart JN, RoseMeyer RB (2019) Biomarkers for the identification of cardiac fibroblast and myofibroblast cells. Heart Fail Rev 24(1):1–15. https://doi.org/10.1007/s10741-018-9720-1
Theivendran S, Xian H, Qu J et al (2024) A pioglitazone nanoformulation designed for cancer-associated fibroblast reprogramming and cancer treatment. Nano Lett 24(15):4354–4361. https://doi.org/10.1021/acs.nanolett.3c04706
Thiery J (2022) Modulation of the antitumor immune response by cancer-associated fibroblasts: mechanisms and targeting strategies to hamper their immunosuppressive functions. Explor Target Anti-Tumor Ther 3(5):598–629. https://doi.org/10.37349/etat.2022.00103
Thinyakul C, Sakamoto Y, Shimoda M et al (2024) Hippo pathway in cancer cells induces NCAM1+αSMA+ fibroblasts to modulate tumor microenvironment. Commun Biol 7(1):1343. https://doi.org/10.1038/s42003-024-07041-4
Thorlacius-Ussing J, Jensen C, Nissen NI et al (2024) The collagen landscape in cancer: profiling collagens in tumors and in circulation reveals novel markers of cancer-associated fibroblast subtypes. J Pathol 262(1):22–36. https://doi.org/10.1002/path.6207
Tian H, Wang W, Liang S, Ding J, Hua D (2024) From darkness to light: targeting CAFs as a new potential strategy for cancer treatment. Int Immunopharmacol 143(Pt 2):113482. https://doi.org/10.1016/j.intimp.2024.113482
Timperi E, Croizer H, Khantakova D et al (2024) At the interface of tumor-associated macrophages and fibroblasts: immune-suppressive networks and emerging exploitable targets. Clin Cancer Res off J Am Assoc Cancer Res. https://doi.org/10.1158/1078-0432.CCR-24-1690
Toledo B, Picon-Ruiz M, Marchal JA, Perán M (2022) Dual role of fibroblasts educated by tumour in cancer behavior and therapeutic perspectives. Int J Mol Sci 23(24):15576. https://doi.org/10.3390/ijms232415576
Tomassetti C, Insinga G, Gimigliano F, Morrione A, Giordano A, Giurisato E (2024) Insights into CSF-1R expression in the tumor microenvironment. Biomedicines 12(10):2381. https://doi.org/10.3390/biomedicines12102381
Tong X, Tang R, Xiao M et al (2022) Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. J Hematol OncolJ Hematol Oncol 15(1):174. https://doi.org/10.1186/s13045-022-01392-3
Truffi M, Mazzucchelli S, Bonizzi A et al (2019) Nano-strategies to target breast cancer-associated fibroblasts: rearranging the tumor microenvironment to achieve antitumor efficacy. Int J Mol Sci 20(6):1263. https://doi.org/10.3390/ijms20061263

Tsai YT, Li CY, Huang YH et al (2022) Galectin-1 orchestrates an inflammatory tumor-stroma crosstalk in hepatoma by enhancing TNFR1 protein stability and signaling in carcinoma-associated fibroblasts. Oncogene 41(21):3011–3023. https://doi.org/10.1038/s41388-022-02309-7

Tsoumakidou M (2023) The advent of immune stimulating CAFs in cancer. Nat Rev Cancer 23(4):258–269. https://doi.org/10.1038/s41568-023-00549-7

Vaish U, Jain T, Are AC, Dudeja V (2021) Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma: an update on heterogeneity and therapeutic targeting. Int J Mol Sci 22(24):13408. https://doi.org/10.3390/ijms222413408

Vienot A, Pallandre JR, Renaude E et al (2022) Chemokine switch regulated by TGF-β1 in cancer-associated fibroblast subsets determines the efficacy of chemo-immunotherapy. Oncoimmunology 11(1):2144669. https://doi.org/10.1080/2162402X.2022.2144669

von Ahrens D, Bhagat TD, Nagrath D, Maitra A, Verma A (2017) The role of stromal cancer-associated fibroblasts in pancreatic cancer. J Hematol OncolJ Hematol Oncol 10(1):76. https://doi.org/10.1186/s13045-017-0448-5

Wang H, Li J, Wang Y et al (2020) Nanoparticles-mediated reoxygenation strategy relieves tumor hypoxia for enhanced cancer therapy. J Control Release off J Control Release Soc 319:25–45. https://doi.org/10.1016/j.jconrel.2019.12.028

Wang B, Zhang Y, Yin X (2023a) Advances in tumor immunomodulation based on nanodrug delivery systems. Front Immunol 14:1297493. https://doi.org/10.3389/fimmu.2023.1297493

Wang L, Wu M, Pan Y et al (2023b) Sequential targeting biomimetic nano platform for enhanced mild photothermal therapy and chemotherapy of tumor. Comput Struct Biotechnol J 21:2780–2791. https://doi.org/10.1016/j.csbj.2023.04.024

Wang T, Ding G, Wang X et al (2024a) Expression of EPB41L2 in cancer-associated fibroblasts: prognostic implications for bladder cancer and response to immunotherapy. Arch Med Res 55(1):102927. https://doi.org/10.1016/j.arcmed.2023.102927

Wang M, Xue W, Yuan H, Wang Z, Yu L (2024b) Nano-drug delivery systems targeting CAFs: a promising treatment for pancreatic cancer. Int J Nanomed 19:2823–2849. https://doi.org/10.2147/IJN.S451151

Wang W, Li T, Xie Z et al (2024c) Integrating single-cell and bulk RNA sequencing data unveils antigen presentation and process-related CAFS and establishes a predictive signature in prostate cancer. J Transl Med 22(1):57. https://doi.org/10.1186/s12967-023-04807-y

Wang B, Pan Y, Xie Y et al (2024d) Metabolic and immunological implications of MME+CAF-mediated hypoxia signaling in pancreatic cancer progression: therapeutic insights and translational opportunities. Biol Proced Online 26(1):29. https://doi.org/10.1186/s12575-024-00254-1

Wang R, Song W, Zhu J et al (2024e) Biomimetic nano-chelate diethyldithiocarbamate Cu/Fe for enhanced metalloimmunity and ferroptosis activation in glioma therapy. J Control Release off J Control Release Soc 368:84–96. https://doi.org/10.1016/j.jconrel.2024.02.004

Wang H, Chen Y, Wei R et al (2024f) Synergistic chemoimmunotherapy augmentation via sequential nanocomposite hydrogel-mediated reprogramming of cancer-associated fibroblasts in osteosarcoma. Adv Mater Deerfield Beach Fla 36(15):e2309591. https://doi.org/10.1002/adma.202309591

Wei R, Song J, Pan H, Liu X, Gao J (2024) CPT1C-positive cancer-associated fibroblast facilitates immunosuppression through promoting IL-6-induced M2-like phenotype of macrophage. Oncoimmunology 13(1):2352179. https://doi.org/10.1080/2162402X.2024.2352179

Wu J, Jing X, Du Q et al (2023) Disruption of the clock component bmal1 in mice promotes cancer metastasis through the PAI-1-TGF-β-myoCAF-dependent mechanism. Adv Sci Weinh Baden-Wurtt Ger 10(24):e2301505. https://doi.org/10.1002/advs.202301505

Wu Y, Chen R, Ni S, Hu K (2024) Biomimetic, "nano-spears" for CAFs-targeting: splintered three "shields" with enhanced cisplatin anti-TNBC efficiency. J Control Release off J Control Release Soc 370:556–569. https://doi.org/10.1016/j.jconrel.2024.04.053

Xia Y, Wang X, Lin J et al (2024) Gastric cancer fibroblasts affect the effect of immunotherapy and patient prognosis by inducing micro-vascular production. Front Immunol 15:1375013. https://doi.org/10.3389/fimmu.2024.1375013

Xiang X, Niu YR, Wang ZH, Ye LL, Peng WB, Zhou Q (2022) Cancer-associated fibroblasts: vital suppressors of the immune response in the tumor microenvironment. Cytokine Growth Factor Rev 67:35–48. https://doi.org/10.1016/j.cytogfr.2022.07.006

Xin L, Gao J, Zheng Z et al (2021) Fibroblast activation protein-α as a target in the bench-to-bedside diagnosis and treatment of tumors: a narrative review. Front Oncol 11:648187. https://doi.org/10.3389/fonc.2021.648187

Xu T, Liu Z, Huang L, Jing J, Liu X (2022) Modulating the tumor immune microenvironment with nanoparticles: a sword for improving the efficiency of ovarian cancer immunotherapy. Front Immunol 13:1057850. https://doi.org/10.3389/fimmu.2022.1057850

Xu Y et al (2023) Fibroblast diversity and plasticity in the tumor microenvironment: roles in immunity and relevant therapies. Cell Commun Signal 21:234

Xu W, Wang K, Wang K, Zhao Y, Yang Z, Li X (2024a) Key magnetized exosomes for effective targeted delivery of doxorubicin against breast cancer cell types in mice model. Int J Nanomed 19:10711–10724. https://doi.org/10.2147/IJN.S479306

Xu N, Wu J, Wang W et al (2024b) Anti-tumor therapy of glycyrrhetinic acid targeted liposome co-delivery of doxorubicin and berberine for hepatocellular carcinoma. Drug Deliv Transl Res 14(9):2386–2402. https://doi.org/10.1007/s13346-023-01512-7

Xu D, Guo D, Zhang J et al (2024c) Innovative tumor interstitial fluid-triggered carbon dot-docetaxel nanoassemblies for targeted drug delivery and imaging of HER2-positive breast cancer. Int J Pharm 657:124145. https://doi.org/10.1016/j.ijpharm.2024.124145

Xue X, Wang X, Pang M et al (2024) An exosomal strategy for targeting cancer-associated fibroblasts mediated tumors desmoplastic microenvironments. J Nanobiotechnol 22(1):196. https://doi.org/10.1186/s12951-024-02452-1

Yamamoto Y, Kasashima H, Fukui Y, Tsujio G, Yashiro M, Maeda K (2023) The heterogeneity of cancer-associated fibroblast subpopulations: their origins, biomarkers, and roles in the tumor microenvironment. Cancer Sci 114(1):16–24. https://doi.org/10.1111/cas.15609

Yamashita K, Kumamoto Y (2024) CAFs-associated genes (CAFGs) in pancreatic ductal adenocarcinoma (PDAC) and novel therapeutic strategy. Int J Mol Sci 25(11):6003. https://doi.org/10.3390/ijms25116003
Yang M, Li J, Gu P, Fan X (2021) The application of nanoparticles in cancer immunotherapy: targeting tumor microenvironment. Bioact Mater 6(7):1973–1987. https://doi.org/10.1016/j.bioactmat.2020.12.010
Yang M, Qin C, Tao L et al (2023a) Synchronous targeted delivery of TGF-β siRNA to stromal and tumor cells elicits robust antitumor immunity against triple-negative breast cancer by comprehensively remodeling the tumor microenvironment. Biomaterials 301:122253. https://doi.org/10.1016/j.biomaterials.2023.122253
Yang D, Liu J, Qian H, Zhuang Q (2023b) Cancer-associated fibroblasts: from basic science to anticancer therapy. Exp Mol Med 55(7):1322–1332. https://doi.org/10.1038/s12276-023-01013-0
Yang M, Li H, Liu X et al (2023c) Fe-doped carbon dots: a novel biocompatible nanoplatform for multi-level cancer therapy. J Nanobiotechnol 21(1):431. https://doi.org/10.1186/s12951-023-02194-6
Yao H, Xu K, Zhou J, Zhou L, Wei S (2020) A tumor microenvironment destroyer for efficient cancer suppression. ACS Biomater Sci Eng 6(1):450–462. https://doi.org/10.1021/acsbiomaterials.9b01544
Yavuz BG, Pestana RC, Abugabal YI et al (2020) Origin and role of hepatic myofibroblasts in hepatocellular carcinoma. Oncotarget 11(13):1186–1201. https://doi.org/10.18632/oncotarget.27532
Yazdimamaghani M, Kolupaev OV, Lim C et al (2025) Tumor microenvironment immunomodulation by nanoformulated TLR 7/8 agonist and PI3k delta inhibitor enhances therapeutic benefits of radiotherapy. Biomaterials 312:122750. https://doi.org/10.1016/j.biomaterials.2024.122750
Ye C, Li WJ, Yu HH et al (2020) Binary blended co-delivery nanoparticles with the characteristics of precise pH-responsive acting on tumor microenvironment. Mater Sci Eng C Mater Biol Appl 117:111370. https://doi.org/10.1016/j.msec.2020.111370
Ye Z, Liu J, Liu Y et al (2024) Hybrid nanopotentiators with dual cascade amplification for glioma combined interventional therapy. J Control Release off J Control Release Soc 372:95–112. https://doi.org/10.1016/j.jconrel.2024.06.016
Yin J, Yuan J, Li Y et al (2023) Neoadjuvant adebrelimab in locally advanced resectable esophageal squamous cell carcinoma: a phase 1b trial. Nat Med 29(8):2068–2078. https://doi.org/10.1038/s41591-023-02469-3
Yin J, Zhu W, Feng S, Yan P, Qin S (2024) The role of cancer-associated fibroblasts in the invasion and metastasis of colorectal cancer. Front Cell Dev Biol 12:1375543. https://doi.org/10.3389/fcell.2024.1375543
Ying F, Chan MSM, Lee TKW (2023) Cancer-associated fibroblasts in hepatocellular carcinoma and cholangiocarcinoma. Cell Mol Gastroenterol Hepatol 15(4):985–999. https://doi.org/10.1016/j.jcmgh.2023.01.006
Yong SB, Chung JY, Song Y, Kim J, Ra S, Kim YH (2019) Non-viral nano-immunotherapeutics targeting tumor microenvironmental immune cells. Biomaterials 219:119401. https://doi.org/10.1016/j.biomaterials.2019.119401
You CQ, Wu HS, Gao ZG et al (2018) Subcellular co-delivery of two different site-oriented payloads based on multistage targeted polymeric nanoparticles for enhanced cancer therapy. J Mater Chem B 6(42):6752–6766. https://doi.org/10.1039/c8tb02230e
Yu Q, Qiu Y, Li J et al (2020) Targeting cancer-associated fibroblasts by dual-responsive lipid-albumin nanoparticles to enhance drug perfusion for pancreatic tumor therapy. J Control Release off J Control Release Soc 321:564–575. https://doi.org/10.1016/j.jconrel.2020.02.040
Yuan CS, Deng ZW, Qin D, Mu YZ, Chen XG, Liu Y (2021) Hypoxia-modulatory nanomaterials to relieve tumor hypoxic microenvironment and enhance immunotherapy: where do we stand? Acta Biomater 125:1–28. https://doi.org/10.1016/j.actbio.2021.02.030
Yuan WC, Zhang JX, Chen HB et al (2023) A bibliometric and visual analysis of cancer-associated fibroblasts. Front Immunol 14:1323115. https://doi.org/10.3389/fimmu.2023.1323115
Yunna C, Mengru H, Fengling W, Lei W, Weidong C (2021) Emerging strategies against tumor-associated fibroblast for improved the penetration of nanoparticle into desmoplastic tumor. Eur J Pharm Biopharm off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV 165:75–83. https://doi.org/10.1016/j.ejpb.2021.05.007
Zang S, Huang K, Li J et al (2022) Metabolic reprogramming by dual-targeting biomimetic nanoparticles for enhanced tumor chemo-immunotherapy. Acta Biomater 148:181–193. https://doi.org/10.1016/j.actbio.2022.05.045
Zare I, Zirak Hassan Kiadeh S, Varol A et al (2024) Glycosylated nanoplatforms: from glycosylation strategies to implications and opportunities for cancer theranostics. J Control Release off J Control Release Soc. 371:158–178. https://doi.org/10.1016/j.jconrel.2024.05.032
Zeltz C, Alam J, Liu H et al (2019) α11β1 integrin is induced in a subset of cancer-associated fibroblasts in desmoplastic tumor stroma and mediates in vitro cell migration. Cancers 11(6):765. https://doi.org/10.3390/cancers11060765
Zeng F, Gao M, Liao S, Zhou Z, Luo G, Zhou Y (2023a) Role and mechanism of CD90+ fibroblasts in inflammatory diseases and malignant tumors. Mol Med Camb Mass 29(1):20. https://doi.org/10.1186/s10020-023-00616-7
Zeng W, Xiong L, Wu W et al (2023b) CCL18 signaling from tumor-associated macrophages activates fibroblasts to adopt a chemoresistance-inducing phenotype. Oncogene 42(3):224–237. https://doi.org/10.1038/s41388-022-02540-2
Zhang Y, Ge J (2020) Green nanoparticles for oligonucleotide delivery. Gene Ther 27(12):535–536. https://doi.org/10.1038/s41434-020-0173-5
Zhang Y, Wang Z, Gemeinhart RA (2013) Progress in microRNA delivery. J Control Release off J Control Release Soc 172(3):962–974. https://doi.org/10.1016/j.jconrel.2013.09.015
Zhang C, Yan L, Gu Z, Zhao Y (2019) Strategies based on metal-based nanoparticles for hypoxic-tumor radiotherapy. Chem Sci 10(29):6932–6943. https://doi.org/10.1039/c9sc02107h
Zhang H et al (2020a) CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. Mol Cancer 19:43
Zhang LY, Zhang JG, Yang X, Cai MH, Zhang CW, Hu ZM (2020b) Targeting tumor immunosuppressive microenvironment for the prevention of hepatic cancer: applications of Traditional Chinese Medicines in targeted delivery. Curr Top Med Chem 20(30):2789–2800. https://doi.org/10.2174/1568026620666201019111524
Zhang Y, Elechalawar CK, Hossen MN et al (2021) Gold nanoparticles inhibit activation of cancer-associated fibroblasts by disrupting communication from tumor and microenvironmental cells. Bioact Mater 6(2):326–332. https://doi.org/10.1016/j.bioactmat.2020.08.009

Zhang T, Yin C, Fedorov A et al (2022a) ADAR1 masks the cancer immunotherapeutic promise of ZBP1-driven necroptosis. Nature 606(7914):594–602. https://doi.org/10.1038/s41586-022-04753-7
Zhang Z, Wang Z, Xiong Y et al (2022b) A two-pronged strategy to alleviate tumor hypoxia and potentiate photodynamic therapy by mild hyperthermia. Biomater Sci 11(1):108–118. https://doi.org/10.1039/d2bm01691e
Zhang H, Yue X, Chen Z et al (2023a) Define cancer-associated fibroblasts (CAFs) in the tumor microenvironment: new opportunities in cancer immunotherapy and advances in clinical trials. Mol Cancer 22(1):159. https://doi.org/10.1186/s12943-023-01860-5
Zhang J, Lu S, Lu T et al (2023b) Single-cell analysis reveals the COL11A1+ fibroblasts are cancer-specific fibroblasts that promote tumor progression. Front Pharmacol 14:1121586. https://doi.org/10.3389/fphar.2023.1121586
Zhang Z, Ding C, Sun T, Wang L, Chen C (2023c) Tumor therapy strategies based on microenvironment-specific responsive nanomaterials. Adv Healthc Mater 12(20):e2300153. https://doi.org/10.1002/adhm.202300153
Zhang Y, Han X, Wang K et al (2023d) Co-delivery nanomicelles for potentiating TNBC immunotherapy by synergetically reshaping CAFs-mediated tumor stroma and reprogramming immunosuppressive microenvironment. Int J Nanomed 18:4329–4346. https://doi.org/10.2147/IJN.S418100
Zhang Y, Pei P, Zhou H et al (2023e) Nattokinase-mediated regulation of tumor physical microenvironment to enhance chemotherapy, radiotherapy, and CAR-T therapy of solid tumor. ACS Nano 17(8):7475–7486. https://doi.org/10.1021/acsnano.2c12463
Zhang H, Chen L, Zhao Y et al (2023f) Relaxin-encapsulated polymeric metformin nanoparticles remodel tumor immune microenvironment by reducing CAFs for efficient triple-negative breast cancer immunotherapy. Asian J Pharm Sci 18(2):100796. https://doi.org/10.1016/j.ajps.2023.100796
Zhang Y, Rahman MM, Clark PA et al (2023g) In situ vaccination following intratumoral injection of IL2 and poly-l-lysine/iron oxide/CpG nanoparticles to a radiated tumor site. ACS Nano 17(11):10236–10251. https://doi.org/10.1021/acsnano.3c00418
Zhang Y, Liu Y, Li T et al (2024a) Engineered bacteria breach tumor physical barriers to enhance radio-immunotherapy. J Control Release off J Control Release Soc 373:867–878. https://doi.org/10.1016/j.jconrel.2024.07.076
Zhang X, Zhang X, Yong T, Gan L, Yang X (2024b) Boosting antitumor efficacy of nanoparticles by modulating tumor mechanical microenvironment. EBioMedicine 105:105200. https://doi.org/10.1016/j.ebiom.2024.105200
Zhang X, Lao M, Yang H et al (2024c) Targeting cancer-associated fibroblast autophagy renders pancreatic cancer eradicable with immunochemotherapy by inhibiting adaptive immune resistance. Autophagy 20(6):1314–1334. https://doi.org/10.1080/15548627.2023.2300913
Zhang X, Zhu R, Yu D, Wang J, Yan Y, Xu K (2024d) Single-cell RNA sequencing to explore cancer-associated fibroblasts heterogeneity: "Single" vision for "heterogeneous" environment. Cell Prolif 57(5):e13592. https://doi.org/10.1111/cpr.13592
Zhang F, Cheng K, Zhang XS et al (2024e) Cascade-catalysed nanocarrier degradation for regulating metabolism homeostasis and enhancing drug penetration on breast cancer. J Nanobiotechnol 22(1):680. https://doi.org/10.1186/s12951-024-02948-w
Zhang Y, Fang Z, Pan D et al (2024f) Dendritic polymer-based nanomedicines remodel the tumor stroma: improve drug penetration and enhance antitumor immune response. Adv Mater Deerfield Beach Fla 36(25):e2401304. https://doi.org/10.1002/adma.202401304
Zhang Y, Yu R, Zhao C et al (2024g) CAFs homologous biomimetic liposome bearing BET inhibitor and pirfenidone synergistically promoting antitumor efficacy in pancreatic ductal adenocarcinoma. Adv Sci Weinh Baden-Wurtt Ger 11(1):e2305279. https://doi.org/10.1002/advs.202305279
Zhang G, Deng L, Jiang Z et al (2024h) Titanium nanoparticles released from orthopedic implants induce muscle fibrosis via activation of SNAI2. J Nanobiotechnol 22(1):522. https://doi.org/10.1186/s12951-024-02762-4
Zhao G, Rodriguez BL (2013) Molecular targeting of liposomal nanoparticles to tumor microenvironment. Int J Nanomed 8:61–71. https://doi.org/10.2147/IJN.S37859
Zhao X, Pan J, Li W, Yang W, Qin L, Pan Y (2018) Gold nanoparticles enhance cisplatin delivery and potentiate chemotherapy by decompressing colorectal cancer vessels. Int J Nanomed 13:6207–6221. https://doi.org/10.2147/IJN.S176928
Zhao T, Zhou H, Lei L et al (2020) A new tandem peptide modified liposomal doxorubicin for tumor "ecological therapy." Nanoscale 12(5):3359–3369. https://doi.org/10.1039/c9nr09585c
Zhao Z, Li T, Yuan Y, Zhu Y (2023) What is new in cancer-associated fibroblast biomarkers? Cell Commun Signal CCS 21(1):96. https://doi.org/10.1186/s12964-023-01125-0
Zhao X, Lin J, Liu M et al (2024) Targeting FAP-positive chondrocytes in osteoarthritis: a novel lipid nanoparticle siRNA approach to mitigate cartilage degeneration. J Nanobiotechnol 22(1):659. https://doi.org/10.1186/s12951-024-02946-y
Zhen Z, Tang W, Wang M et al (2017) Protein nanocage mediated fibroblast-activation protein targeted photoimmunotherapy to enhance cytotoxic T cell infiltration and tumor control. Nano Lett 17(2):862–869. https://doi.org/10.1021/acs.nanolett.6b04150
Zheng D, Wan C, Yang H et al (2020) Her2-targeted multifunctional nano-theranostic platform mediates tumor microenvironment remodeling and immune activation for breast cancer treatment. Int J Nanomed 15:10007–10028. https://doi.org/10.2147/IJN.S271213
Zheng S, Wang J, Ding N et al (2021) Prodrug polymeric micelles integrating cancer-associated fibroblasts deactivation and synergistic chemotherapy for gastric cancer. J Nanobiotechnol 19(1):381. https://doi.org/10.1186/s12951-021-01127-5
Zheng Z, Duan A, Dai R et al (2022) A "dual-source, dual-activation" strategy for an NIR-II window theranostic nanosystem enabling optimal photothermal-ion combination therapy. Small Weinh Bergstr Ger 18(27):e2201179. https://doi.org/10.1002/smll.202201179
Zheng F, Luo Y, Liu Y, Gao Y, Chen W, Wei K (2023a) Nano-baicalein facilitates chemotherapy in breast cancer by targeting tumor microenvironment. Int J Pharm 635:122778. https://doi.org/10.1016/j.ijpharm.2023.122778

Zheng D, Zhou J, Qian L et al (2023b) Biomimetic nanoparticles drive the mechanism understanding of shear-wave elasticity stiffness in triple negative breast cancers to predict clinical treatment. Bioact Mater 22:567–587. https://doi.org/10.1016/j.bioactmat.2022.10.025
Zheng R, Yu C, Yao D, et al. Engineering stimuli-responsive materials for precision medicine. Small Weinh Bergstr Ger. 2024:e2406439. https://doi.org/10.1002/smll.202406439.
Zhong L, Chen B, He J et al (2021) Focused ultrasound-augmented cancer phototheranostics using albumin-indocyanine green nanoparticles. Ultrasound Med Biol 47(7):1801–1813. https://doi.org/10.1016/j.ultrasmedbio.2021.02.026
Zhou S, Zhen Z, Paschall AV et al (2021) FAP-targeted photodynamic therapy mediated by ferritin nanoparticles elicits an immune response against cancer cells and cancer associated fibroblasts. Adv Funct Mater 31(7):2007017. https://doi.org/10.1002/adfm.202007017
Zhou Z, Li C, Li C et al (2024a) Mitochondria-targeted nanoadjuvants induced multi-functional immune-microenvironment remodeling to sensitize tumor radio-immunotherapy. Adv Sci Weinh Baden-Wurtt Ger 11(26):e2400297. https://doi.org/10.1002/advs.202400297
Zhou X, Cai Q, Zhao S et al (2024b) CDs-ICG@BSA nanoparticles for excellent phototherapy and in situ bioimaging. Talanta 271:125661. https://doi.org/10.1016/j.talanta.2024.125661
Zhu Y, Wen L, Shao S et al (2018) Inhibition of tumor-promoting stroma to enforce subsequently targeting AT1R on tumor cells by pathological inspired micelles. Biomaterials 161:33–46. https://doi.org/10.1016/j.biomaterials.2018.01.023
Zhu Z, McGray AJR, Jiang W, Lu B, Kalinski P, Guo ZS (2022) Improving cancer immunotherapy by rationally combining oncolytic virus with modulators targeting key signaling pathways. Mol Cancer 21(1):196. https://doi.org/10.1186/s12943-022-01664-z
Zhu Y, Wang A, Zhang S et al (2023) Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells. J Adv Res 49:159–173. https://doi.org/10.1016/j.jare.2022.09.007
Zu Y, Wang Z, Yao H, Yan L (2023) Oxygen-generating biocatalytic nanomaterials for tumor hypoxia relief in cancer radiotherapy. J Mater Chem B 11(14):3071–3088. https://doi.org/10.1039/d2tb02751h

Publisher's Note