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Cancer remains one of the most challenging health issues globally, demanding innovative therapeutic approaches for effective treatment. Nanoparticles, particularly those composed of gold, silver, and iron oxide, have emerged as promising candidates for changing cancer therapy. This comprehensive review demonstrates the landscape of nanoparticle-based oncological interventions, focusing on the remarkable advancements and therapeutic potentials of gold, silver, and iron oxide nanoparticles. Gold nanoparticles have garnered significant attention for their exceptional biocompatibility, tunable surface chemistry, and distinctive optical properties, rendering them ideal candidates for various cancer diagnostic and therapeutic strategies. Silver nanoparticles, renowned for their antimicrobial properties, exhibit remarkable potential in cancer therapy through multiple mechanisms, including apoptosis induction, angiogenesis inhibition, and drug delivery enhancement. With their magnetic properties and biocompatibility, iron oxide nanoparticles offer unique cancer diagnosis and targeted therapy opportunities. This review critically examines the recent advancements in the synthesis, functionalization, and biomedical applications of these nanoparticles in cancer therapy. Moreover, the challenges are discussed, including toxicity concerns, immunogenicity, and translational barriers, and ongoing efforts to overcome these hurdles are highlighted. Finally, insights into the future directions of nanoparticle-based cancer therapy and regulatory considerations, are provided aiming to accelerate the translation of these promising technologies from bench to bedside.

1. Introduction

Cancer, a complex disease, presents a formidable challenge to global health systems and societies due to its complicated nature characterized by uncontrolled cell growth and proliferation.[1–6] This complexity highlights the critical need for early diagnosis and intervention to reduce disease progression and severity. Detecting cancer at its early stages is essential for enabling timely and efficacious therapeutic interventions, potentially preventing the complications and therapeutic challenges associated with advanced-stage malignancies. Despite substantial advancements in elucidating the molecular pathways driving cancer initiation and progression, as well as the development of various therapeutic approaches, including surgical resection, chemotherapeutics, radiation therapy, and immunomodulatory treatments, cancer therapy continues to face significant challenges. A major obstacle in cancer therapy is the intrinsic heterogeneity of malignancies, which manifests both across different cancer types and within individual tumors. This heterogeneity arises from variations in genetic mutations, cellular phenotypes, tumor microenvironmental factors, and differential therapeutic responses,

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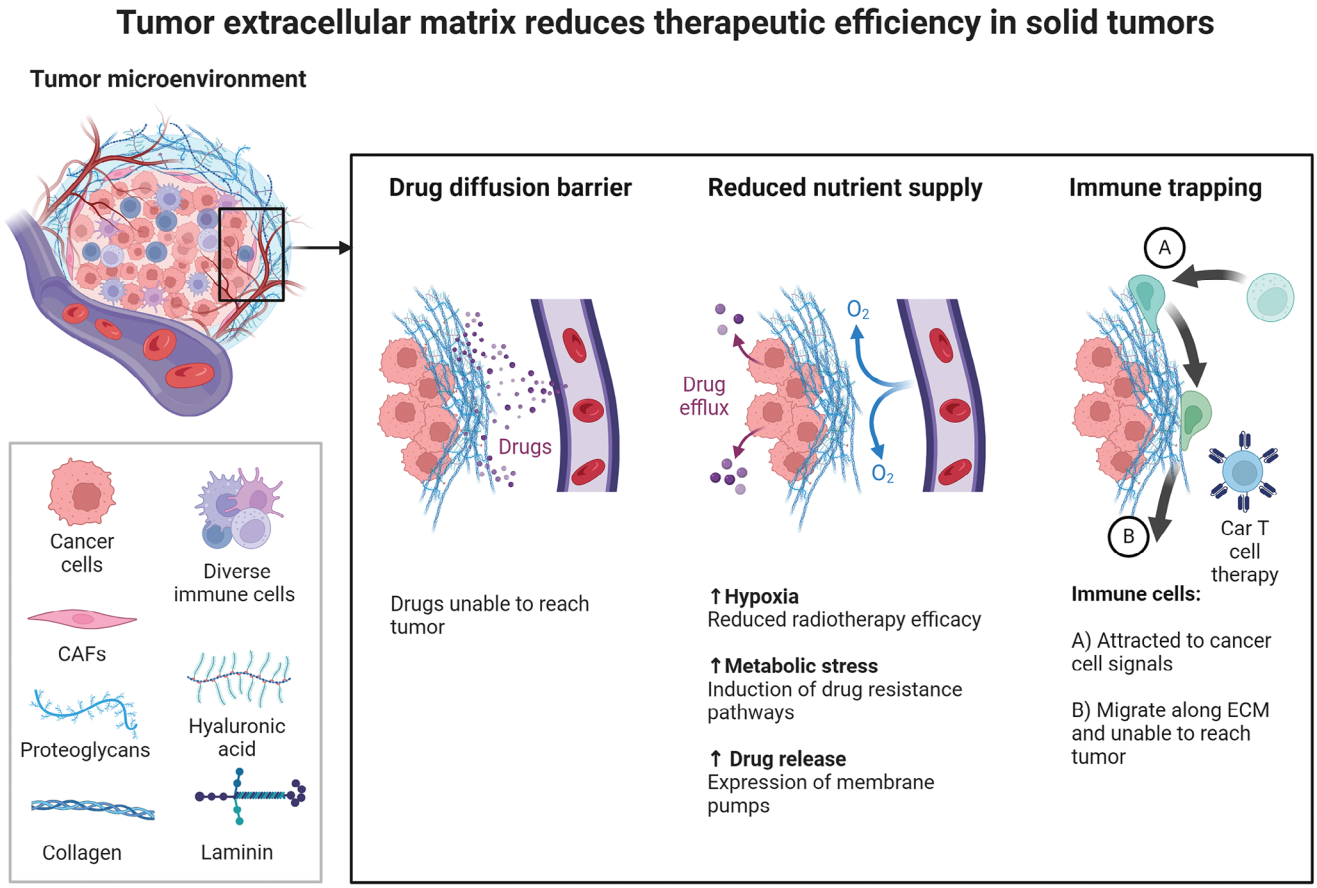

Figure 1. Interaction of drugs and tumor microenviroment (TME). The tumor extracellular matrix (ECM) creates barriers that reduce therapeutic efficiency in solid tumors. Dense ECM hinders drug diffusion, and induces hypoxia and metabolic stress, leading to drug resistance and reduced radiotherapy efficacy. Immune cells, such as CAR T cells, are either trapped by tumor signals or obstructed by the ECM, preventing effective tumor targeting. http://biorender.com.

necessitating tailored, patient-specific diagnostic and treatment approaches.[7]

Moreover, the evolution of cancer over time adds another layer of complexity. Tumors undergo genetic alterations, leading to therapeutic resistance, recurrence, and disease progression. This necessitates molecular surveillance and adaptive treatment strategies to counteract tumor evolution and resistance mechanisms.[8] The tumor-immune system interaction presents additional challenges.[9] While immunotherapy has shown significant promise in mobilizing the immune system to eliminate cancer cells, some patients exhibit limited or no response to these treatments, underscoring the need for improved immune-targeting strategies.[10] This underscores the need for a deeper understanding of the tumor-immune microenvironment and the identification of biomarkers predictive of immunotherapy efficacy. Ongoing challenges include understanding the intricate dynamics of the tumor-immune microenvironment and identifying biomarkers predictive of immunotherapy response. Moreover, socioeconomic disparities, geographical location, healthcare infrastructure, and cultural differences further complicate cancer management by limiting access to care and contributing to unequal outcomes.[6,11] Therefore, the heterogeneity and multifactorial nature of cancer pose substantial challenges to global healthcare systems. Overcoming these barriers requires an integrated approach that combines basic and translational research, innovative diagnostic tools, personalized therapies, and equitable access to comprehensive cancer care.

In addition to the systemic challenges posed by the heterogeneity and multifactorial nature of cancer, the tumor microenvironment (TME) introduces further obstacles to effective treatment. The TME, with its unique biological composition, significantly influences tumor growth, therapeutic response, and resistance. A key component of the TME is the extracellular matrix (ECM), which plays a pivotal but often underexplored role in tumor progression and therapeutic resistance. As described in **Figure 1**, solid tumors trigger the overproduction of ECM molecules such as collagens, proteoglycans, hyaluronic acid, and laminins, leading to a dense and disorganized ECM structure. One key role of the ECM is acting as a physical barrier for delivering therapeutic agents, nutrients, and immune cells to the tumor site.[12] This results in reduced treatment efficacy. To address this issue, there is a critical need for the development of innovative tools or technologies capable of penetrating and persisting within the hostile environment of the TME. Such technologies must be engineered to withstand the stressful conditions

encountered within tumors without causing unintended side effects.

In recent decades, nanotechnology has emerged as a promising frontier in cancer research and therapy, offering novel solutions to address the limitations of traditional treatments.[13] Nanoparticles, defined as structures with dimensions at the nanoscale, possess unique physicochemical properties, including high surface area-to-volume ratio, tunable optical, magnetic, and electronic properties, and the ability to interact with biological systems at the molecular level.[14,15] Advances in nanoparticle synthesis, surface engineering, and biomedical applications have facilitated the development of sophisticated nanoparticle-based therapeutics with enhanced targeting specificity, therapeutic efficacy, and safety profiles.[16] By using these properties, nanoparticles can overcome numerous biological barriers that hinder conventional therapies. These include navigating the tumor's complex microenvironment, evading immune surveillance, and facilitating efficient cellular uptake. Nanoparticles can be engineered to enhance drug retention and accumulation within tumors through mechanisms such as the enhanced permeation and retention (EPR) effect while improving the delivery of precision therapies, including CAR T cell treatments, EGFR-targeted therapies, and RNA-based therapeutics (**Figure 2**). These versatile applications highlight the potential of nanoparticles to significantly propel advancements in precision medicine, accelerating clinical translation and enabling more personalized therapeutic strategies.

1.1. Understanding the Enhanced Permeability and Retention (EPR) Effect

The EPR effect is a cornerstone of nanoparticle-based therapies, enabling the selective accumulation of therapeutic agents within tumors due to their abnormal vasculature. Unlike healthy tissues, tumor blood vessels are irregular, disorganized, and possess larger gaps between endothelial cells, allowing nanoparticles within the 10–200 nm size range to penetrate and accumulate more effectively. Additionally, tumors exhibit poor lymphatic drainage, further enhancing nanoparticle retention in the tumor microenvironment. This leads to a higher localized concentration of therapeutic agents at the tumor site, reducing off-target effects and improving overall treatment efficacy. Nanoparticle systems such as metallic nanoparticles, liposomes, polymeric micelles, and dendrimers are engineered with surface modifications to evade immune detection and improve circulation time, optimizing tumor targeting. Upon accumulation, these nanoparticles can deliver their therapeutic payload in a controlled manner, maximizing therapeutic outcomes. However, the efficacy of the EPR effect varies depending on factors such as tumor type, stage, and microenvironment, making it a crucial consideration in designing nanoparticle-based cancer therapies.[17]

Additionally, combining nanoparticles with other treatment modalities, such as chemotherapy, immunotherapy, and radiotherapy, offers the potential for synergistic therapeutic effects and improved patient outcomes. Nanoparticles offer a unique advantage in their ability to navigate the complex and hostile environment of the TME. While free drugs are smaller, nanoparticles offer additional advantages, such as improved circulation time, targeted delivery, and the ability to overcome biological barriers, allowing them to accumulate more effectively in the TME than conventional therapies. Their small size allows them to penetrate the dense ECM and reach cancer cells more effectively. Additionally, surface modifications can be engineered to enhance nanoparticle stability, prolong circulation time, and promote specific targeting of cancer cells while minimizing off-target effects (**Figure 3**).[1] This targeted delivery ensures that therapeutic payloads are delivered precisely to the tumor site, maximizing efficacy while minimizing systemic toxicity. Additionally, nanoparticles can be designed to exploit the unique characteristics of the TME. For example, stimuli-responsive nanoparticles can release their payload in response to specific cues like changes in pH, temperature, or enzyme activity.[18] This "smart" drug delivery strategy provides precise control over drug release kinetics, enhancing therapeutic outcomes while reducing adverse effects on healthy tissues.[19] Furthermore, nanoparticles' multifunctionality allows them to deliver multiple therapeutic or imaging contrast agents simultaneously, paving the way for theranostic applications in personalized cancer care. This combination of diagnostic and therapeutic functionalities enables real-time monitoring of treatment response and customized therapy adjustments for each patient.[20]

Among various nanoparticle platforms, Gold nanoparticles (AuNPs), Silver nanoparticles (AgNPs), and Iron oxide nanoparticles (IONPs) have garnered considerable attention for their distinct characteristics and versatile applications in oncology.[21] AuNPs are renowned for their exceptional biocompatibility, inertness, and ease of surface functionalization, making them ideal candidates for cancer diagnostics and treatments. The surface plasmon resonance (SPR) property of AuNPs enables selective absorption and scattering of light, which has been harnessed for various diagnostic imaging techniques, including surface-enhanced Raman scattering (SERS) and photoacoustic imaging.[22] Additionally, AuNPs exhibit strong photothermal properties, allowing for localized hyperthermia treatment through photothermal therapy (PTT), wherein the nanoparticles absorb near-infrared (NIR) light and convert it into heat to ablate cancer cells.[23,24]

AgNPs possess antimicrobial properties, attributed to their high surface area and the release of silver ions, which disrupt microbial cell membranes and inhibit their growth.[25] In cancer therapy, AgNPs have demonstrated promising anticancer activity through multiple mechanisms, including induction of apoptosis, angiogenesis inhibition, and drug delivery enhancement.[26] Moreover, AgNPs exhibit synergistic effects when combined with conventional chemotherapeutic agents, leading to improved therapeutic outcomes and reduced systemic toxicity.[27]

IONPs are characterized by their magnetic properties, biocompatibility, and ease of functionalization, making them valuable tools for cancer diagnosis, imaging, and therapy.[28,29] Superparamagnetic iron oxide nanoparticles (SPIONs) are commonly employed as contrast agents in magnetic resonance imaging (MRI) due to their ability to alter the relaxation times of surrounding water protons, thereby enhancing tissue contrast.[30] Moreover, IONPs can be functionalized with targeting ligands or therapeutic payloads for site-specific drug delivery and magnetic hy-

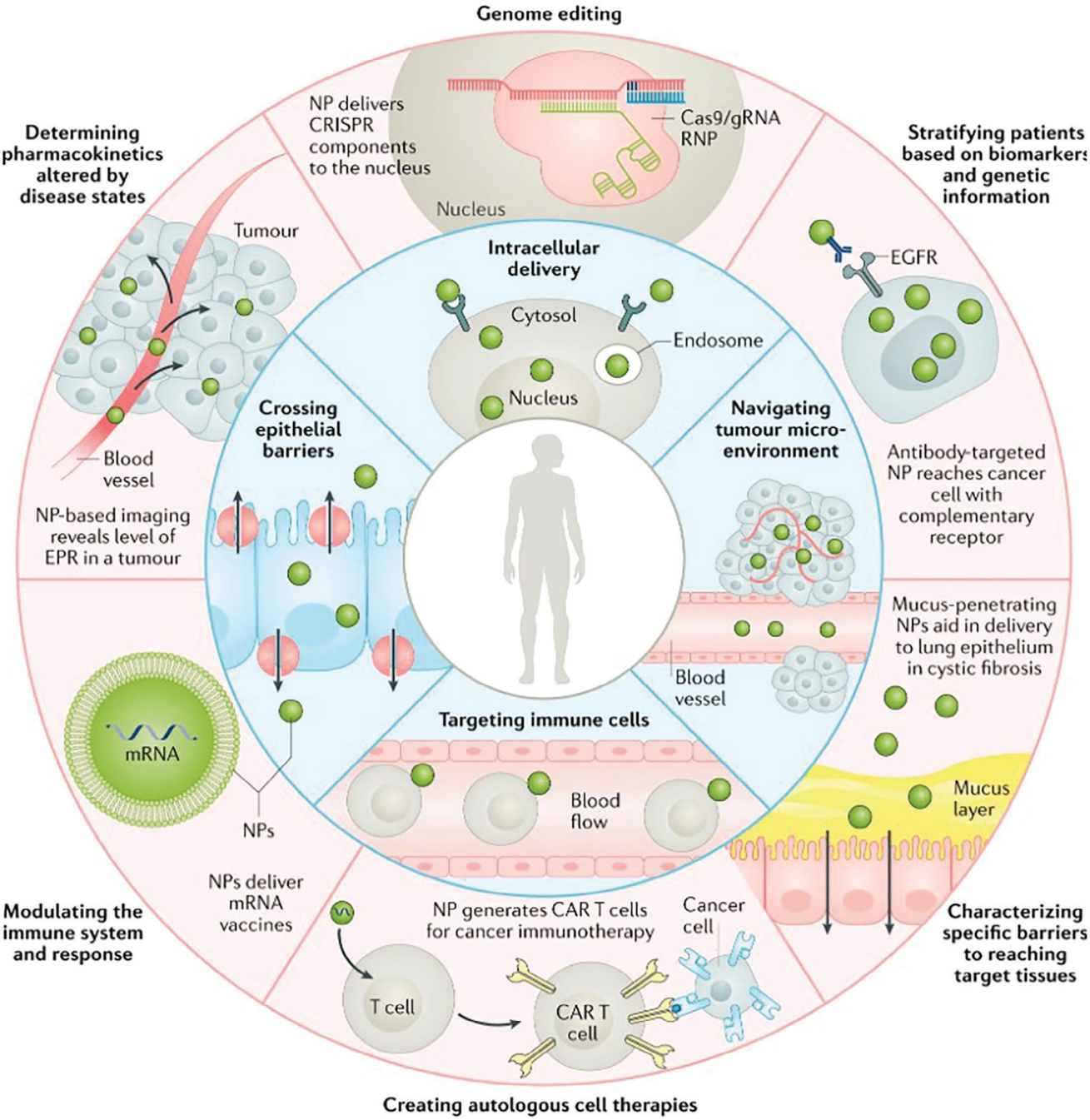

Figure 2. Overview of the biological barriers that nanoparticles can overcome (inner ring) and precision medicine applications that may benefit from nanoparticles (outer ring). Intelligent nanoparticle designs can navigate cellular uptake challenges, immune system evasion, and targeted tissue delivery, thus enhancing drug delivery mechanisms. Applications include chimeric antigen receptor (CAR) therapies, epidermal growth factor receptor (EGFR)-targeted treatments, EPR effect, and delivery of guide RNA (gRNA) and ribonucleoprotein (RNP) complexes. These advancements have the potential to accelerate the clinical translation of precision medicines. Reproduced Copyright Nature Reviews Drug Discovery 2021.[2]

perthermia therapy, wherein alternating magnetic fields (AMF) induce localized heating of tumor tissues containing magnetic nanoparticles.[31]

However, despite the significant progress, several challenges and considerations must be addressed to realize the full potential of nanoparticle-based cancer therapy. These include concerns regarding nanoparticle toxicity, biocompatibility, immunogenicity, pharmacokinetics, and regulatory approval processes. Moreover, translating nanoparticle-based therapeutics from preclinical studies to clinical applications necessitates rigorous validation, standardization, and optimization of manufacturing processes, formulation strategies, and clinical trial designs.

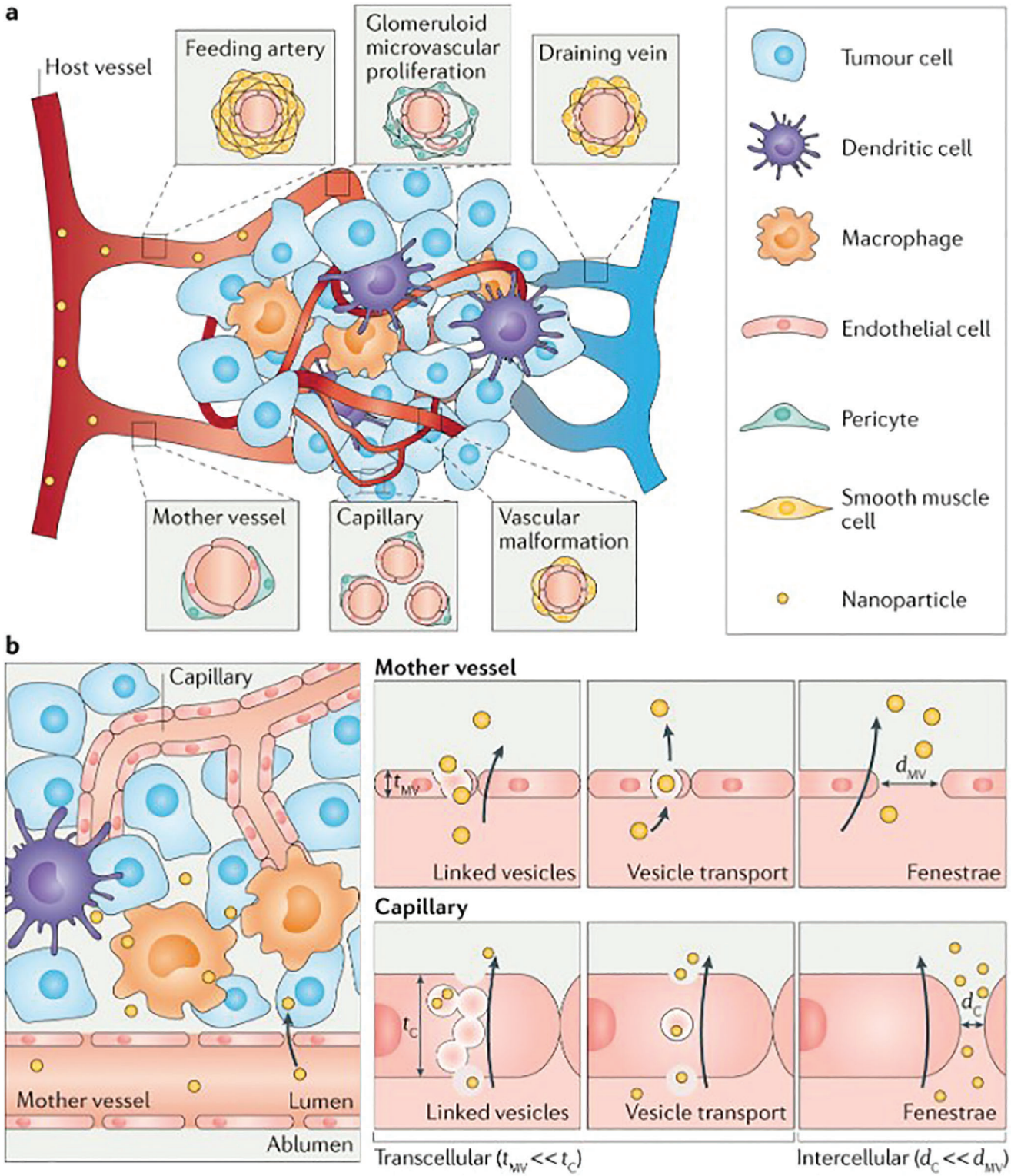

Figure 3. In the interendothelial cell extravasation mechanism, nanoparticles are transported through gaps of 100–500 nm in diameter. d_C, the intercellular gap distance in capillaries; d_{MV}, the intercellular gap distance in mother vessels; t_C, the thickness of endothelial cells lining the capillaries; t_{MV}, the thickness of endothelial cells lining the mother vessels. Copyright Nature Reviews 2016.[1]

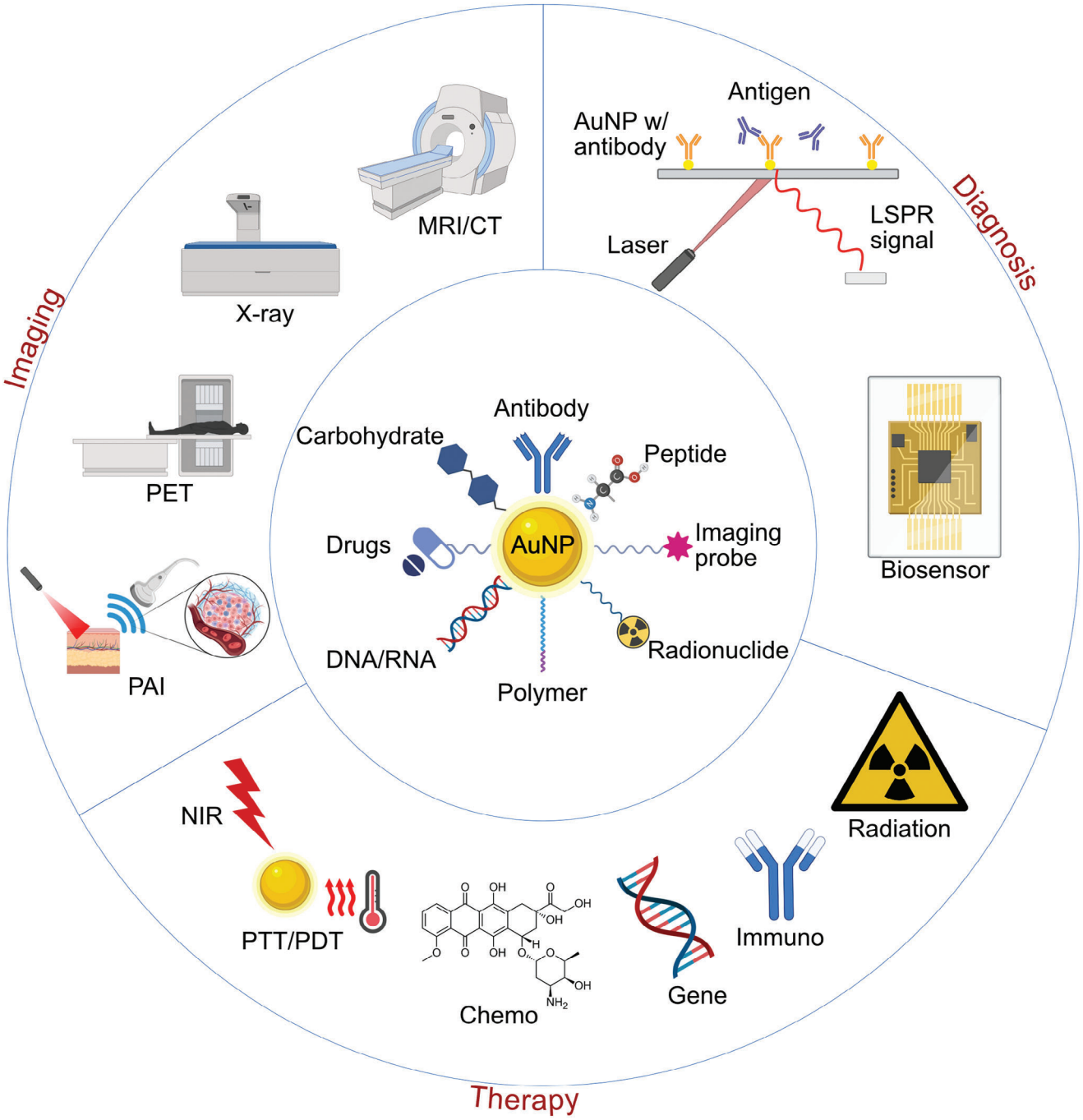

Figure 4. Application of AuNPs in cancer diagnosis, imaging, and therapy.

In this comprehensive review, we aim to examine the ability of gold, silver, and iron oxide nanoparticles in oncological applications. We elucidate these nanoparticles' diverse roles and therapeutic potentials in cancer diagnosis, imaging, and therapy by critically analyzing the latest research findings, technological developments, and clinical advancements. Furthermore, we explore the challenges, opportunities, and future directions of nanoparticle-based cancer therapy with the aim of advancing the clinical application of these innovative technologies, improving patient outcomes, and driving progress in the field of oncology.

2. Gold Nanoparticles

AuNPs have emerged as a revolutionary platform for cancer theranostics, offering a unique combination of diagnostic and therapeutic capabilities. Their unique size-dependent optical properties make them ideal for in vivo imaging modalities.[23] At the

same time, their high surface area-to-volume ratio allows for the conjugation of therapeutic agents and targeting moieties. **Figure 4** illustrates various applications of AuNPs in the context of cancer. This section delves into the exciting potential of AuNPs in cancer management, exploring their applications in both diagnosis and therapy.

2.1. Physicochemical Properties

The size, shape, and surface characteristics of AuNPs play a crucial role in determining their behavior in biological systems, including their interaction with cancer cells, cellular uptake, biodistribution, and toxicity.[32] Herein, we discuss the role of size, shape, and surface characteristics in dictating the behavior of AuNPs within the context of cancer.

2.1.1. Size

The size of AuNPs is an essential property that affects their interaction with the biological environment. AuNPs can range from 1 to 100 nm, and this parameter significantly impacts their biodistribution, cellular internalization, tumor penetration, and therapeutic efficacy.[33,34] Smaller AuNPs are preferred for drug delivery applications requiring intracellular release of therapeutic cargo as they exhibit a higher surface-to-volume ratio, allowing for increased interaction with biological molecules.[35] Studies have shown smaller AuNPs have higher cellular uptake and better tumor penetration than larger particles.[36,37] AuNPs with a size of 25.5 nm were efficient in inducing cell death and toxicity in cervical cancer cells.[38] Conversely, larger AuNPs are better suited for targeted imaging as they can evade renal clearance, leading to prolonged circulation times and enhanced accumulation in tumor sites through the EPR effect. Smaller AuNPs tend to be rapidly cleared from the body through renal excretion, while larger nanoparticles are more prone to clearance by the mononuclear phagocyte system (MPS).[39] Thus, the size of AuNPs is a critical factor that governs their pharmacokinetics and biodistribution. Therefore, it is essential to consider the size of AuNPs when designing and developing them for specific applications, as it can significantly impact their effectiveness and safety.

2.1.2. Shape

The shape of AuNPs also plays a critical role in determining their interaction with cellular components and biomolecules, as well as their optical, electronic, and biological properties.[40] While spherical AuNPs are the most common, anisotropic-shaped AuNPs like rods, triangles, cages, and stars have potential applications in cancer diagnosis and treatment.[41] Gold nanorods, for example, exhibit tunable SPR absorption in the near-infrared (NIR) region, enabling deep tissue penetration and PTT of tumors.[42] Gold nanocages, with their hollow interiors and porous shells, can serve as efficient drug-delivery vehicles and contrast agents for multimodal imaging.[43] Star-shaped nanoparticles have shown improved drug-loading capabilities compared to their spherical counterparts.[44] Additionally, anisotropic-shaped nanoparticles demonstrate shape-dependent cellular uptake mechanisms and intracellular distribution patterns, affecting their therapeutic efficacy and toxicity profiles.[45,46] The shape of AuNPs can also impact their cellular internalization, intracellular trafficking, and biodistribution, with some shapes exhibiting preferential accumulation in specific organs or tumor sites. Therefore, understanding and controlling the shape of AuNPs is essential for developing effective cancer therapeutics and diagnostics.

2.1.3. Surface Characteristics

Another important physicochemical property of AuNPs is their surface characteristics, which include surface charge and functionalization. The surface charge of AuNPs plays a crucial role in their interaction with biological membranes and proteins.[47,48] Positively charged AuNPs have been shown to have higher cellular uptake compared to negatively charged particles.[49,50] The free Au atoms on their surface also make AuNPs highly amenable to surface modifications. Such modifications include functionalization with biomolecules like peptides and antibodies and polymers like polyethylene glycol (PEG). AuNPs can also be designed to respond to internal or external stimuli to enable controlled drug release. Surface modifications with biocompatible coatings (e.g., PEGylation, silica) improve their stability, biocompatibility, and circulation half-life, reducing non-specific protein adsorption and immune recognition.[51] Furthermore, attaching targeting ligands like antibodies or peptides to the surface of AuNPs allows for specific binding to cancer biomarkers, reducing side effects on healthy tissue and facilitating targeted imaging and therapy.[38]

2.2. Synthesis Methods

The synthesis of AuNPs plays a vital role in determining their efficacy in cancer applications. Over the years, several synthesis methods have been developed, each with its advantages and limitations. In this context, we present a comprehensive review of the recent synthesis methods specifically designed for cancer applications.

2.2.1. Classical Synthesis Method

Chemical reduction is widely used for synthesizing AuNPs due to its simplicity and reproducibility.

2.2.2. Turkevic/Frens

Turkevich introduced the classical synthesis method for AuNPs in 1951, which was improved by Frens in 1972. This reaction involves reducing chlorauric acid ($HAuCl_4$ $4H_2O$) with sodium citrate in an aqueous solution.[52,53] Recent modifications of this method have focused on controlling the size and monodispersity of the nanoparticles for enhanced tumor targeting and

penetration. For instance, Bouyon et al. demonstrated a high-yield one-step synthesis of small water-soluble AuNPs, offering the potential for improved cancer therapy by improving drug potency and reducing toxic side effects.[36]

2.2.3. Brust–Schiffrin Method

This method utilizes biphasic reduction with a thiol-containing ligand in an organic solvent to synthesize highly stable AuNPs. These particles have tunable sizes and surface functionalities due to the binding of the thiol molecules to the AuNPs surface.[54] In a recent study, Salamone et al. demonstrated the potential of thiol-functionalized AuNPs for effectively delivering the anticancer drug methotrexate (MTX).[55] They concluded that the thiol-functionalized AuNPs-MTX nanoconjugate enhanced drug penetration inside cells compared to free MTX.

2.2.4. Seed-Mediated Growth

The seed-mediated growth approach is another popular method for synthesizing AuNPs. This technique involves using preformed AuNPs seeds as nucleation sites in a growth solution containing gold salts, reducing agents, and stabilizers. It provides precise control over particle size, shape, and aspect ratio, particularly useful for synthesizing anisotropic AuNPs like rods, cubes, or stars. These unique shapes have exceptional optical properties suitable for PTT and PAI in cancer treatment. For instance, Jia et al. synthesized Au nanocorals using seed-mediated growth, having precise control over their localized surface plasmon resonance (LSPR), making them an excellent candidate for PTT and PAI applications.[56] Adjusting certain reaction parameters, such as precursor concentration, reaction temperature, and reaction time, can precisely control the size and shape of AuNPs. This level of control over the synthesis of AuNPs allows for customization of their properties, making them suitable for specific applications.

2.3. Emerging Techniques

2.3.1. Green Synthesis

Green synthesis methods have emerged as a sustainable and eco-friendly alternative to chemical reduction, which uses toxic chemicals.[57] These methods utilize biological materials like bacteria, fungi, plant extracts, proteins, and enzymes as reducing and stabilizing agents. They offer several advantages, such as biocompatibility, scalability, and reduced environmental impact. For instance, AuNPs synthesized using *Viridibacillus* sp. extract have demonstrated potent anticancer activity, making them promising candidates for cancer therapy.[58] Similarly, Pearce et al. utilized plant extract of *Typha capensis* to synthesize AuNPs with inherent anti-cancer properties.[59] These biogenic nanoparticles not only demonstrated cytotoxic effects against cancer cells but also acted as carriers for bioactive compound naringenin, showcasing their potential as dual-function agents in cancer therapy. Moreover, Yan et al. synthesized AuNPs from *Olea europaea* (olive) fruit extract. The nanoparticles exhibited potent anticancer activity against multiple gastric cancer cell lines.[60]

2.3.2. Photochemical Methods

Photochemical methods involve the reduction of gold salts under light irradiation, particularly ultraviolet (UV) or visible light sources. These approaches offer exceptional control over the size, shape, and surface characteristics of AuNPs by modulating variables such as light intensity, wavelength, and reaction time. Additionally, these methods can be combined with other surface functionalization techniques. Photothermal approaches, which rely on light-induced heating to promote the reduction of gold salts, have also been investigated to synthesize AuNPs possessing superior photothermal properties for cancer therapy. For instance, Gomes et al. conducted a study in which they synthesized AuNPs using UV irradiation.[61] The resulting AuNPs were found to have reduced toxicity towards NIH-3T3 fibroblasts and did not cause maternal toxicity in rat models. Furthermore, the AuNPs were tested as a contrast agent for CT and performed similarly to commercially available iodine contrast agents.

2.3.3. Microfluidic Synthesis

Microfluidic synthesis is highly precise and efficient for producing monodisperse AuNPs with customizable properties. This process involves using microchannels to enable precise mixing of reactants for rapid, continuous synthesis of uniform nanoparticles. This approach has been successfully used to fabricate multifunctional AuNPs that can be applied in cancer imaging, drug delivery, and therapy. Advancements in microfluidic platforms, such as integrated surface modification functionalities, offer the potential for high-throughput synthesis of application-specific AuNPs. For instance, Dalibera et al. demonstrated that AuNPs of varying size and morphology can be synthesized using a microfluid reactor for potential application in cancer diagnosis and therapy.[62] Similarly, Perez Schmidt synthesized ultrasmall AuNPs by combining microfluidics and photochemical methods, allowing simultaneous functionalization of the AuNPs.[63] Additionally, Meincke & Klupp Taylor utilized a microfluidic reactor to form plasmonic Au patches on polystyrene particles having tunable optical properties, opening avenues for cancer theranostics.[64]

2.3.4. Template-Assisted Synthesis

Template-assisted synthesis is a technique used to produce AuNPs with uniform and well-defined structures. This method involves using pre-designed templates or scaffolds to guide and control the growth of NPs, resulting in greater control over their morphology and functionality.[65] Templates, such as surfactant micelles, polymers, dendrimers, mesoporous silica, or biomolecules like DNA, have been utilized to control AuNPs' size, shape, and assembly. By selecting appropriate templates, AuNPs with tailored properties can be fabricated for specific cancer applications. This approach has proven useful for creating hollow or cage-like structures that can encapsulate drugs or imaging agents for cancer treatment. In a study by Shang et al., polydopamine/Au hollow spheres were developed using the sacrificial template method.[66] These spheres were highly effective

as multifunctional theranostic agents, capable of providing simultaneous in vitro ultrasound imaging and PTT. Additionally, in 2018, Liu and his team employed an amino-functionalized metal-organic framework as a template to produce porous gold nanoshells capable of carrying various cargo. They successfully demonstrated the application of this system for simultaneous photodynamic and PTT against tumors both in vitro and in vivo.[67] In addition, the authors used polystyrene microspheres as a template to obtain an array of AuNPs with exceptional SERS properties. The system could successfully detect very low concentrations of analyte, thus paving the way for its use as a detection platform for cancer biomarkers. These innovative approaches hold great potential for early cancer diagnosis and personalized medicine.

2.3.5. Laser Ablation

Pulsed laser ablation (PLA) utilizes high-energy laser pulses to ablate a gold target submerged in a liquid medium, resulting in the generation of biocompatible, stable, and monodisperse AuNPs.[68] The ability to control ablation parameters and advancements in laser technology offers new and exciting possibilities for the precise design of AuNPs. These AuNPs have the potential to be used in PTT due to their enhanced ability to absorb light in the NIR region, which can penetrate deep into tissues. When these AuNPs are exposed to NIR light, they convert the absorbed light into heat, enabling localized PTT for cancer cell ablation.[69] Mzwd et al. synthesized AuNPs by PLA using Gum Arabic as a stabilizer.[70] These nanoparticles enhanced the contrast of computed tomography (CT) imaging, showcasing their potential for cancer diagnosis. Similarly, Abdulateef et al. synthesized bovine serum albumin conjugated AuNPs using the PLA technique.[71] The nanoparticles exhibited high biocompatibility and low toxicity towards normal fibroblast cells (L929), indicating their potential application in drug delivery. The study also found that the nanoparticles demonstrated dose-dependent inhibition of HeLa cells, suggesting their promising anticancer activity.

2.3.6. Electrochemical Synthesis

Electrochemical synthesis is another promising method for producing AuNPs in a clean and efficient way. This method involves the electrochemical reduction of gold salts at electrode surfaces, allowing for the controlled synthesis of AuNPs. By controlling the reduction process using parameters such as applied potential, current density, and reaction time, precise control can be achieved over the size, morphology, and surface properties of the AuNPs. For example, Luong et al. developed a method for synthesizing gold nanoflowers using electrochemical synthesis, which was used for SERS detection of rhodamine B.[72] Similarly, J. Wang, Luo, et al. demonstrated an ultrafast, reproducible method for the synthesis of Au@Ag core-shell nanoflowers to be used as a SERS substrate for label-free detection of thiram in milk and juice samples with an ultra-low detection limit.[73] This AuNPs platform has the potential to be used as a SERS substrate for the detection of cancer biomarkers. Moreover, in a study by German et al., dendritic gold nanostructures (DGN) were electrochemically synthesized.[74] These DGNs showed a high sensitivity for detecting glucose in blood serum in the presence of interfering species. This showcases their potential use for the early detection of cancer. Furthermore, multiple studies have highlighted the scope of electrochemical synthesis of AuNPs in a fast, reproducible, and controlled manner, which can have potential applications in cancer theranostics.[75,77]

Thus, AuNPs are increasingly used for cancer diagnosis and treatment, and a diverse range of synthesis methods are available for their fabrication. Traditional techniques are well-established, simple, and versatile while emerging methods offer exciting opportunities for advanced functionalities. The selection of the most suitable method depends on factors such as desired nanoparticle properties, scalability, and biocompatibility. The choice of synthesis method can significantly impact the physicochemical properties of the nanoparticles and thus affect their efficacy in cancer diagnosis and treatment. Therefore, continued advancements in synthesis methods and a deeper understanding of their impact on AuNPs behavior are essential for developing next-generation AuNP-based cancer theranostics.

2.4. Applications in Cancer Diagnostics and Monitoring

AuNPs are promising tools for enhancing various imaging modalities in cancer diagnostics and monitoring. Due to their small size, tunable surface functionality, and high biocompatibility, they are ideal for targeted delivery and multimodal imaging capabilities.[78] AuNPs exhibit specific characteristics due to their LSPR, which leads to intense light scattering and/or absorbance.[79] AuNPs can enhance the sensitivity, specificity, and accuracy of imaging techniques such as CT, MRI, PAI, and SERS imaging.[80] The high atomic number, electron density, and X-ray attenuation properties of gold make AuNPs excellent candidates for enhancing the contrast and spatial resolution of CT images.[81] Additionally, the strong binding affinity of gold to thiol and amine groups allows for the surface of AuNPs to be easily functionalized with biomolecules such as DNA, siRNA, peptides, antibodies, and receptors. When functionalized with targeting ligands, AuNPs can selectively accumulate in tumor tissues, allowing for improved visualization and delineation of cancerous regions.[82] This comprehensive analysis explores the diverse applications of AuNPs in cancer imaging, highlighting their contributions to improving diagnostic accuracy, sensitivity, and monitoring capabilities.

2.4.1. Computed Tomography (CT) Imaging

AuNPs have shown great potential as contrast agents for CT imaging, enhancing cancer detection and staging. This is due to their high atomic number and electron density, which enhances the contrast and spatial resolution of CT scans, enabling early detection and accurate visualization of cancerous lesions. Unlike traditional contrast agents used in CT imaging, which suffer from short circulation times and potential toxicity, AuNPs are biocompatible and have a high X-ray attenuation coefficient, enabling improved contrast enhancement and localization of tumors in CT imaging, thus making them a promising alternative.[83,84] AuNPs can be functionalized with high-Z elements such as gadolinium, which attenuate X-rays to a greater

extent, leading to a brighter contrast than surrounding tissues.[85] This enhanced contrast facilitates the detection of smaller tumors and improves the visualization of tumor margins.

Recent studies have demonstrated the potential of AuNPs for CT-based cancer imaging. In a study by Danesh-Doust et al., they developed a novel nanoprobe by coating AuNPs with alginate and functionalizing them with the Triptorelin peptide.[86] The Triptorelin-modified AuNPs were then used to target MCF-7 cells that overexpress GnRH receptors. The researchers found that conjugating Triptorelin to the AuNPs increased the accumulation of AuNPs on the tumor surface, enhancing the contrast for CT imaging. Furthermore, B. Jia et al. developed a drug delivery system that combines MTX and AuNPs.[87] The multifunctional system could be used for CT imaging as well as for the controlled release of AuNPs and MTX. The research team demonstrated that the system is effective in cellular uptake and has potent anticancer activity both in vitro and in vivo. Additionally, the AuNPs aided in performing CT imaging of tumors in a mouse model. T. Kim et al. conducted a study involving live mice injected with AuNPs. The mice were subjected to X-ray fluorescence (XRF) and CT imaging techniques to determine the in vivo biodistributions of AuNPs. The study results indicated that the insights obtained could enhance AuNPs-based cancer therapy by reducing accumulation in healthy tissues and increasing the targeting of tumors. Linh et al. synthesized Ag–Au alloy nanoparticles that can be used for biomedical imaging.[88] The nanoparticles displayed remarkable durability and stability and were non-toxic to the Vero cell line. In vitro CT imaging revealed a high X-ray absorption coefficient, indicating their potential as a contrast agent for CT imaging.

2.4.2. Magnetic Resonance Imaging (MRI)

AuNPs have shown great potential in improving the quality of MRI scans.[89] When combined with other elements, they can enhance T1 and T2 relaxation times, which improves the contrast and signal-to-noise ratio in MRI.[90,91] AuNPs complex can act as either T1 or T2 contrast agents depending on the desired imaging effect, which enables targeted visualization of tumors based on their specific cellular environment. This makes it possible to guide minimally invasive cancer therapies such as image-guided surgery or drug delivery using real-time visualization within the body for precise targeting and monitoring of therapeutic procedures.[92] By functionalizing AuNPs with paramagnetic or superparamagnetic materials, their performance as contrast agents for MRI can be enhanced. These multifunctional AuNPs provide anatomical and functional information, allowing for non-invasive and real-time monitoring of cancer progression and response to therapy. This enables better visualization and delineation of tumors, especially when the AuNPs are coated with gadolinium-based chelates and SPIONs for T1 or T2 enhancement.[93] Surface modifications of AuNPs can also enable their accumulation in tumors and improve the sensitivity of MRI for cancer detection. AuNPs can be used to develop multimodal imaging probes for simultaneous MRI and other imaging modalities, providing complementary information for accurate cancer diagnosis. For instance, C. Yang et al. developed gadolinium-functionalized AuNPs that can be used for both MR and CT imaging, as well as for PTT.[94] These nanoparticles exhibited excellent tumor-contrasted imaging performance in both MR and CT imaging modalities and were effective in killing tumor cells in vitro. Moreover, MR/CT imaging-guided PTT using these nanoparticles was successful in ablation of tumor tissues without any systemic toxicity in mouse models. Similarly, Z. Wang et al. reported the development of a targeted system that can be used for multi-mode imaging and enhanced PTT of metastatic prostate cancer (PCa).[95] The system showed outstanding cancer theranostic capabilities as it combines fluorescence, MR, and CT imaging with PTT. The improved recognition by GnRH-R on the surface of PCa cells resulted in enhanced accumulation of the nano-system at the tumor site and improved PCa target specificity. Overall, the system's multifunctionality and targeted approach make it a promising candidate for treating metastatic prostate cancer. Furthermore, J. Wang, Li, et al. developed a Gd-AuNPs multimodal contrast agent functionalized with prostate-specific membrane antigen (PSMA).[96] The system exhibited excellent imaging capabilities in MRI, CT, and NIR fluorescence imaging modalities. The contrast agent also demonstrated high specificity towards PCa cells. Furthermore, the system was found to be efficiently cleared through the renal system, reducing the likelihood of potential toxicities.

2.4.3. Photoacoustic Imaging (PAI)

Another promising application of AuNPs in cancer imaging is their use in PAI. PAI is a non-invasive imaging technique that combines the benefits of high contrast of optical imaging with the deep tissue penetration of ultrasound imaging.[97] It uses laser pulses to generate acoustic waves, which are then detected and used to reconstruct an image. AuNPs exhibit excellent light absorption properties, especially in the NIR region, allowing for highly sensitive and specific detection of cancer cells. When exposed to NIR light, AuNPs can convert absorbed light into heat, generating a localized pressure wave detectable by PAI technology. This allows for deep tissue penetration and high-resolution imaging of tumors. AuNPs of different sizes or surface modifications can be used to create contrast agents that can be differentiated by PAI, enabling the visualization of multiple biomarkers within a tumor or surrounding vasculature and providing richer diagnostic information. This technique has shown promise in tumor vasculature mapping, sentinel lymph node detection, and monitoring of therapeutic responses.[98] I.-C. Sun et al. developed a chitosan-conjugated AuNPs-based PAI contrast agent functionalized with ovalbumin (OVA) epitope.[99] This system demonstrated exceptional capabilities in US/PA imaging of lymph nodes, in addition to delivering tumor antigens for cancer immunotherapy. Similarly, Z. Li et al. reported the synthesis of AuNP-based PA/PTT imaging and cancer therapy systems.[100] This system allowed for NIR-II PA imaging of tumor tissues, and the high-intensity light absorption of AuNRs in the NIR-II region enhanced tumor photothermal imaging and therapy. Furthermore, Geng et al. created a system based on AuNPs to guide radiotherapy using PAI.[101] The system showed increased accumulation and retention in hypoxic tumors, resulting in the aggregation of gold nanospheres, which enabled the use of NIR-II

for PAI and enhanced radiosensitization, thereby increasing the therapeutic effects.

2.4.4. Surface-Enhanced Raman Spectroscopy (SERS)

SERS imaging is a highly sensitive and specific technique that utilizes the SPR of AuNPs to enhance the Raman scattering signals of target molecules. It has been identified as a promising approach for cancer diagnostics and monitoring due to its ability to provide molecular fingerprints of cancer cells.[102] AuNPs can amplify the Raman scattering signal of molecules adsorbed onto their surface, enabling the detection of specific cancer biomarkers in very low concentrations.[103] AuNPs can also be functionalized with antibodies or aptamers specific to cancer cells, allowing them to selectively bind to cancer cells and act as targeted SERS probes that enable the sensitive identification of cancer cells within complex biological samples. Dong et al. successfully developed a theranostic nanosystem that utilizes AuNPs for SERS imaging and gene therapy.[104] The system achieved high specificity and sensitivity through the synergistic effect of target-triggered SERS imaging and DNAzyme-based dual gene-silencing therapy. Similarly, Qiu et al. synthesized Au@Ag core-shell nanoparticles that were highly sensitive in detecting biomarkers expressed on the surface of breast cancer cell lines.[105] The researchers used SERS imaging to distinguish the expression level of the three biomarkers and the cancer cell phenotypes. In addition, the researchers evaluated the therapeutic efficacy of chemotherapy and surgical treatment through SERS imaging. The study's results demonstrated the potential of utilizing SERS imaging for accurate and effective detection of breast cancer and evaluation of its treatment. Furthermore, a theranostic platform was created by R. Jiang et al. for cancer treatment using AuNPs.[106] The platform employed SERS probes based on AuNPs that exhibited a remarkable ability to perform SERS imaging of live cells and dynamic visualization of tumors in a 4T1 breast tumor mouse model. The in vivo studies demonstrated that the system exhibited a potent PTT effect on 4T1 breast tumors under NIR irradiation. These findings suggest that AuNP-based SERS probes have the potential to be used for efficient SERS-guided cancer hyperthermia therapy. Moreover, Y. Tan et al. developed DNA-linked AuNPs for PAI and SERS-based microRNA detection.[107] The system was tested on MCF-7 cells, which have high expression of MiR-21, to evaluate its performance for miRNA imaging. The results showed a strong SERS signal in the MCF-7 cells, while no signal was in the MiR-21 negative expressed cell line, MCF-10A. The authors successfully demonstrated the use of the system for both in vitro and in vivo tumor PAI and SERS imaging.

2.4.5. Optical Imaging

AuNPs possess a strong SPR in the visible and NIR range, which makes them ideal candidates for optical imaging techniques like fluorescence imaging, photoluminescence imaging, and two-photon luminescence imaging.[108] By functionalizing AuNPs with fluorescent dyes or Raman reporters, they can be tailored for targeted tumor visualization and molecular imaging. AuNPs can also be conjugated with fluorescent molecules for in vivo or ex vivo cancer cell imaging.[109,110] In addition to imaging applications, AuNPs can also be used for PTT and imaging concurrently.[111] During PTT, NIR light exposure heats the AuNPs, which can lead to the ablation of cancer cells. Optical imaging can provide real-time feedback on PTT efficacy by monitoring changes in local blood flow or temperature. AuNPs can also act as efficient fluorescence quenchers or enhancers, improving sensitivity and specificity in cancer imaging.[112] Techniques like dark-field (DF) microscopy can also be used with AuNPs to visualize cancer cells.[56,113,114] Besides cancer cell imaging, AuNPs are also used as probes to detect intracellular biological processes, including cell signaling pathways and cell cycles.[115] AuNPs can also be radiolabeled with isotopes, which makes them useful as radiotracers for positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging.[116–118] Compared to traditional radiotracers, AuNPs have longer circulation times, better targeting of tumors, and reduced systemic toxicity. Radiolabeled AuNPs can target specific cancer biomarkers, providing details about tumor metabolism and proliferation.[119]

2.4.6. Multimodal Imaging

AuNPs are highly versatile and can be used with various imaging modalities. The combination of multiple imaging modalities can provide complementary information, thereby enhancing the overall accuracy and specificity of cancer diagnostics.[120] AuNPs can also be integrated into multimodal imaging probes, allowing simultaneous or sequential imaging using different modalities, leading to enhanced sensitivity and specificity for cancer diagnosis and staging. For instance, Pan et al. developed a multifunctional theranostic platform using Au nanocages that could be used for fluorescence, MR, and PA imaging.[121] The platform has been demonstrated to have the ability to inhibit the growth of esophageal cancer by combining PTT, radio, and chemotherapy. Similarly, Gowtham et al. synthesized polymeric hydrogel-encased gold-shelled carbon-coated manganese ferrite nanodots.[122] These nanoparticles were designed to improve encapsulation efficiency, biocompatibility, and multimodal imaging capabilities. The resulting nanoparticles demonstrated dual-mode MRI contrast capabilities and compatibility with CT and fluorescence-based imaging, making them a promising multimodal diagnosis agent. Moreover, Cai et al. developed polydopamine-coated Au/Si core-shell particles that can be used for multimode imaging and PTT of tumors.[123] The platform showed good colloidal stability and cytocompatibility. It displayed excellent PA/ultrasound/CT/thermal imaging capabilities and was effective in photothermal ablation of cancer cells in vitro and in a xenografted 4T1 tumor model in vivo, showcasing their potential for cancer diagnosis and therapy. Overall, AuNPs exhibit remarkable optical properties, which make them a versatile and promising tool for cancer imaging and therapy. Due to their unique properties, AuNPs hold immense potential in comprehensive cancer diagnosis and monitoring and can significantly improve patient outcomes.

2.5. AuNPs in Drug Delivery Strategies

Nanoparticle-based drug delivery systems are a promising approach for targeted drug delivery and controlled release mechanisms in cancer therapy.[124] Among various nanoparticles, AuNPs are gaining popularity as a potential solution for targeted drug delivery and controlled release mechanisms in cancer therapy. Their unique properties, including biocompatibility, biodegradability, and surface functionality, make them an ideal candidate for encapsulating and delivering a wide range of therapeutic agents, such as chemotherapeutic drugs, nucleic acids, and antibodies. Recent advancements have demonstrated their potential to improve the efficacy and specificity of cancer treatment while minimizing systemic toxicity. By functionalizing the surface of AuNPs with targeting ligands, researchers have demonstrated enhanced accumulation of AuNPs in tumor tissues. AuNPs can specifically target cancer cells and deliver therapeutic agents at a controlled rate. Furthermore, they can enhance the therapeutic efficacy of drugs by improving their pharmacokinetics and pharmacodynamics.[125] This part presents a detailed exploration of the use of AuNPs in cancer treatment, emphasizing their applications in targeted drug delivery and controlled release strategies.

2.5.1. Targeted Drug Delivery

Traditional cancer therapies often lack selectivity, leading to severe side effects.[126] A key objective in oncology is to deliver drugs directly to cancer cells while minimizing systemic toxicity. AuNPs have become a promising platform for targeted cancer therapy, utilizing both active and passive targeting mechanisms to specifically target tumors.

2.5.2. Passive targeting

AuNPs exploit the EPR effect, a phenomenon where leaky tumor vasculature and impaired lymphatic drainage allow for the accumulation of nanoparticles within the tumor site.[127] This passive targeting mechanism takes advantage of the aberrant TME, facilitating the preferential accumulation of AuNPs at the tumor site while minimizing systemic distribution to healthy tissues. In a recent study, Gu et al., created a tetrahedral DNA stacked AuNPs loaded with Doxorubicin (DOX), a commonly used chemotherapy drug.[128] The researchers found that these nanoparticles could accumulate in the tumor through the EPR effect and release the drug cargo in response to the acidic environment of the tumor, resulting in effective anticancer activity.

2.5.3. Active Targeting

Researchers have thoroughly investigated active targeting strategies by modifying the surface of AuNPs with specific ligands, including antibodies, peptides, or aptamers, to enable precise delivery to cancer cells that overexpress specific receptors.[129] These ligands recognize and bind to specific biomarkers on the surface of cancer cells, enabling selective uptake of AuNPs and subsequent release of therapeutic payloads within the TME. For instance, Emami et al. designed a novel approach for targeting colorectal cancer cells using anti-PD-L1 antibodies and DOX-conjugated AuNPs.[130] This strategy enabled targeted delivery to the cancer cells and improved the intracellular retention of DOX. Combined with NIR irradiation for PTT, the approach resulted in successful cell cycle arrest and induced apoptosis and necrosis in the CT-26 cells. Similarly, He et al. developed a NIR-II imaging and therapeutic platform by synthesizing AuNPs functionalized with dual targeting ligands loaded with oxaliplatin (OX), allowing for rapid tumor accumulation and prolonged retention.[131] The system enabled controlled OX release and induced tumor cell apoptosis in 4T1 cells overexpressing spermine (SPM) while offering simultaneous imaging capabilities. Furthermore, the platform demonstrated minimal toxicity to normal cells (HK-2) with lower SPM expression and exhibited efficient renal clearance.

Recent studies have demonstrated the successful delivery of chemotherapeutic agents, siRNA, and photothermal agents using AuNPs conjugated with specific ligands for targeted cancer therapy. For instance, Żelechowska-Matysiak et al. developed AuNPs conjugated with anti-HER2 antibodies (trastuzumab) and loaded with DOX for targeted chemo-PTT of HER2-positive breast cancer.[132] This approach demonstrated enhanced cellular uptake and improved therapeutic efficacy. Heris et al. designed polydopamine-coated AuNPs for siRNA delivery to prostate cancer cells (PC3).[133] The AuNPs facilitated the delivery of siRNA against the EGFR gene, leading to gene silencing and tumor growth inhibition. Tunç & Aydin designed an AuNPs-based delivery system to co-deliver Bcl-2 siRNA & DOX.[134] The system was tested against two breast cancer cell lines (MDA-MB-231 & MCF7), resulting in the effective inhibition of Bcl-2 expression and significant cytotoxicity. Similarly, Ren et al. developed AuNPs functionalized with folic acid (FA) and loaded with paclitaxel (PTX) for targeted delivery to folate receptor-overexpressing cancer cells.[135] The FA-AuNP-PTX system exhibited good target selectivity and enhanced cytotoxicity in four cancer cell lines (HL-7702, Hela, SMMC-7721, and HCT-116), highlighting its potential for targeted cancer therapy. Additionally, Ibarra et al. reported the synthesis of PLGA-AuNPs conjugated with a cyclic RGD peptide and loaded with PTX for targeting integrin-overexpressing cancer cells (HeLa and MDA-MB-231).[136] The RGD-AuNP-PTX system demonstrated improved tumor accumulation and therapeutic efficacy in vitro, having a sustained release profile that could be altered with laser irradiation. Furthermore, Y. Yang et al. developed aptamer functionalized Au nanocages for the targeted co-delivery of siRNA & DOX for a combination of genetic, chemo, and PTT against lung cancer cells (NCI-H889).[137] The nanosystem effectively silenced the target gene while delivering chemotherapy drugs and PTT to inhibit tumor progression. In vivo experiments showed that the nanosystem significantly increased survival rates in mice. Thus, we can conclude that AuNPs provide a high surface area for conjugating multiple therapeutic agents, targeting ligands, or imaging probes.

2.5.4. Controlled Release

AuNPs can also be used to encapsulate or conjugate therapeutic agents and release them in a controlled manner in response to external stimuli or physiological triggers. This enables precise spatiotemporal control over drug release, enhancing therapeu-

tic efficacy and reducing systemic toxicity.[138] Various strategies have been explored to modulate the release kinetics of drugs from AuNPs, including stimuli-responsive systems and surface modifications. Internal or external stimuli can trigger controlled release from AuNPs carriers, enabling targeted drug delivery to tumor sites. Internal stimuli, such as variations in pH or redox gradients within the TME, can initiate drug release from AuNPs.[139] Similarly, external stimuli, including light, ultrasound, or magnetic fields, can trigger drug release from AuNPs upon exposure to specific wavelengths or frequencies.[140] AuNPs can be modified to respond to specific stimuli, such as:

- pH: Tumors have an acidic microenvironment compared to healthy tissues.[141] pH-sensitive AuNPs can be designed to release drugs when they come across this acidic environment, minimizing toxicity to healthy cells. For instance, Chauhan et al. developed γ-globulin functionalized, pH-responsive AuNPs that can deliver DOX and enhance cytotoxicity against cancer cells (C6 glioma) in acidic conditions.[142] Similarly, Luan et al. developed a pH-responsive AuNPs delivery system.[143] This system exhibited acid-triggered aggregation, prolonged retention in tumor tissue, and enhanced sensitivity to radiation therapy while also enabling the controlled release of the chemotherapy drug DOX. The system was tested on esophageal cancer cells (KYSE-510) and showed promising results for potentially treating this type of cancer. By utilizing the acidic microenvironment of tumors, pH-sensitive AuNPs can ensure selective drug release within cancer cells while sparing healthy tissues, thus reducing off-target effects and systemic toxicity.
- Temperature: Thermoresponsive AuNPs are sensitive to temperature and can release drugs in response to heat. This heat can be generated intrinsically within the TME or applied externally using NIR irradiation. AuNPs can be functionalized with heat-sensitive polymers that undergo conformational changes in response to mild hyperthermia, commonly associated with tumors.[144] Upon exposure to increased temperatures, these polymers facilitate controlled drug release from AuNPs, thus enhancing therapeutic efficacy while minimizing premature drug release in normal physiological conditions. García et al. developed pH and temperature-responsive AuNPs for the delivery of DOX.[145] The nanoparticles exhibited an increased release of DOX under acidic conditions and hyperthermia, indicating their potential use in cancer treatment. Moreover, the research findings also demonstrated the system's promising anticancer activity against breast cancer (MDA-MB-231) and ovarian cancer cells (SK-OV-3). Similarly, D. Kim et al. created Au-collagen hydrogel nanoparticles that respond to light and temperature to deliver therapeutic proteins inside cells.[146] The system demonstrated high loading efficiency and controlled release when subjected to external stimuli, indicating its potential as an effective approach for anticancer therapy.
- Light: Photo-responsive AuNPs can be triggered by light to release drugs. This approach is a subcategory of the thermo-responsive release strategy and is often combined with PTT, where AuNPs generate heat upon NIR irradiation, causing localized cell ablation and controlled drug release. By taking advantage of the NIR responsiveness of AuNPs, researchers can achieve precise on-demand drug release, which maximizes therapeutic outcomes. For Instance, J. Zhang et al. synthesized photo-responsive AuNPs to deliver DOX.[147] In addition to being pH and temperature-responsive, the release rate of DOX could be accelerated by NIR irradiation. In vitro experiments confirmed the combined effect of chemotherapy and PTT on cancer cells (HepG2). Similarly, Consoli et al. devised a biocompatible, photo-responsive delivery system.[148] The system integrates AuNP, graphene oxide, and thermo-sensitive polymer and can be activated by red-light excitation of 680 nm wavelength to achieve controlled drug release of curcumin via photothermal heating. Furthermore, Bergueiro et al. developed a NIR-stimulated AuNPs drug delivery system for the delivery of DOX.[149] In vitro tests using HeLa cells demonstrated a low cell viability with the system. Additionally, in vivo studies on mice showed that the system inhibited tumor growth.

Several recent studies highlight the potential of AuNPs for stimuli-responsive release of cargo for anticancer therapy: Quazi & Park developed a photothermal-peptide drug delivery system.[150] The system contained a cell-penetrating anticancer peptide drug and a cancer-targeting peptide. AuNPs acted as photothermal reagents for light-triggered peptide drug release. The nanocomplex was found to specifically target cancer cells and release anticancer peptide drugs to kill them with negligible hazardous effects on normal cell lines. Kalyane et al. synthesized a NIR-responsive AuNPs-based targeted drug delivery system for the controlled delivery of DOX.[151] The system demonstrated NIR-responsive and pH-dependent drug release behavior, indicating its potential for chemo-PTT. Moreover, it exhibited CD-44 receptor-specific uptake and significant cytotoxicity against MDA-MB-231 breast cancer cells. L. Liu et al. reported the synthesis of temperature, pH, and light-responsive folic acid conjugated AuNPs.[152] They tested the system for the controlled delivery of the drug DOX against 4T1 breast cancer cells. The results showed that the system was biocompatible, as it prevented the premature release of the drug. It also demonstrated target specificity and significant cytotoxicity against the cancer cells, indicating its potential as an effective drug delivery system for cancer treatment. Nori et al. developed an AuNP-based multimodal cancer therapy system that featured gold-coated magnetic nanoparticles and a thiol-containing dendrimer loaded with the anticancer drug 6-mercaptopurine (6-MP).[153] The system was designed to release the drug in a controlled manner in the acidic environment of cancer cells, leading to high toxicity against MCF-7 cells. Moreover, the system had the potential to improve the contrast of MR images and generate hyperthermia upon PTT. Overall, the system demonstrated great potential as a multifunctional theranostic platform that can offer drug delivery, PTT, and MRI contrasting capabilities. **Figure 5** illustrates a strategy for co-delivering chemotherapeutic drugs and siRNA using AuNPs to treat pancreatic cancer. The system can shield the cargo from enzymatic degradation and release them in a controlled manner under internal/external stimuli such as acidic TME or NIR irradiation, thereby enhancing the sensitivity and improving the treatment outcome. Another study demonstrated the use of a bacterial biomineralization-generated immunomodulator, "Ausome" (Au + [exo]some), which combines a gold nanoparticle core with bacterial components to enhance tumor immune responses. The

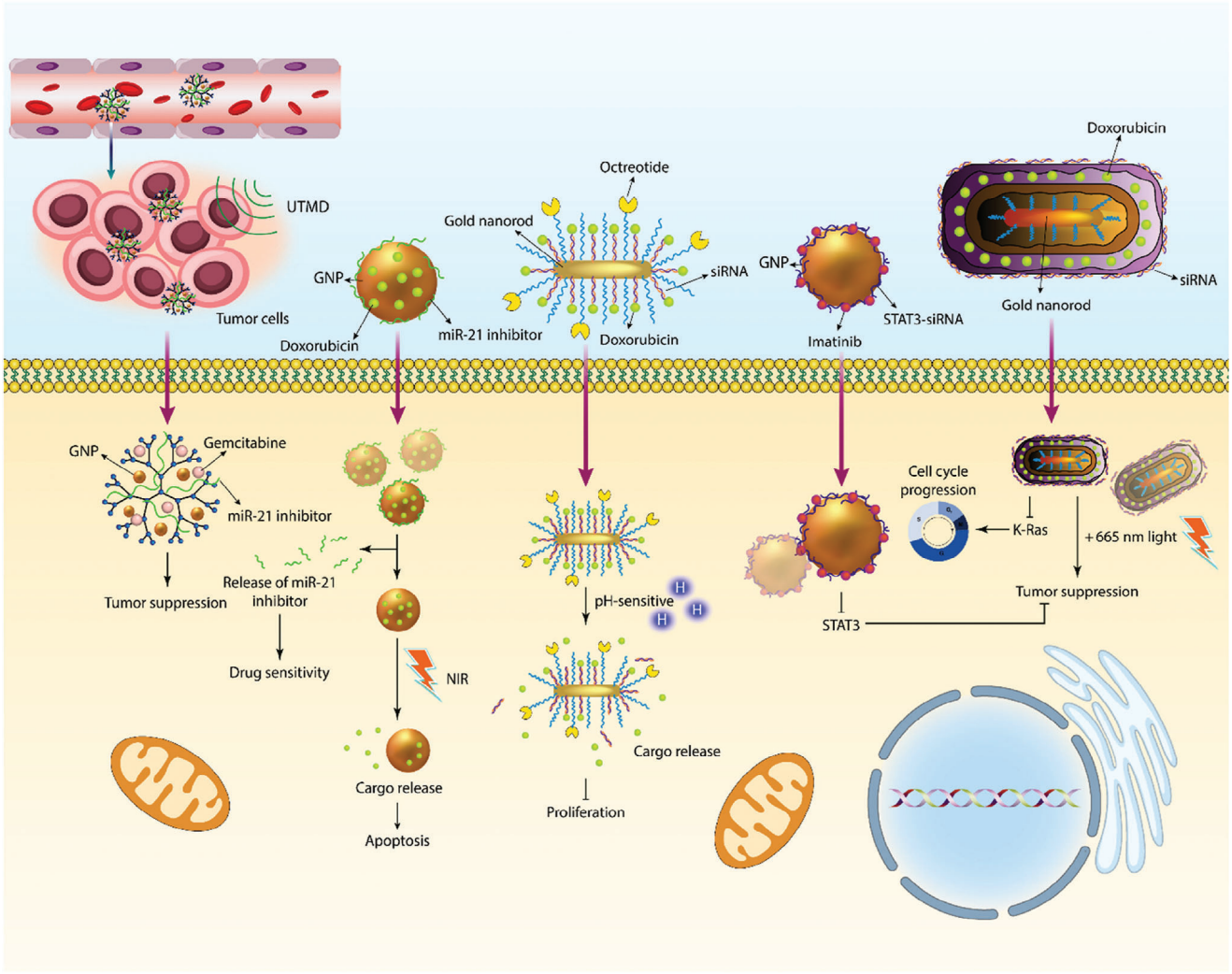

Figure 5. AuNPs-based stimuli-responsive drug delivery system for the co-delivery of siRNA and chemotherapeutic drugs against pancreatic tumour cells. Copyright Environmental Research 2023.[4]

gold core induces hyperthermia upon laser irradiation, while the bacterial components trigger immune activation by stimulating pattern recognition receptors (PRRs). Upon intravenous administration, Ausome initiates a systemic immune response, and when exposed to laser irradiation at the tumor site, it enhances local immune infiltration and amplifies antitumor activity by improving tissue perfusion and vascular permeability (**Figure 6**). This strategy offers advantages over traditional immunotherapies by focusing on localized immune modulation, minimizing systemic side effects. Preclinical models have shown that Ausome significantly boosts the efficacy of chemo- and immunotherapies by promoting a more active tumor immune microenvironment. Further research is needed to optimize its clinical application for cancer treatment.[3] Such advancements underscore the transformative potential of AuNPs in cancer therapy, where their stimuli-responsive designs for controlled drug release significantly boost therapeutic efficiency while reducing systemic toxicity. As these nanoparticle technologies evolve, they continue to present promising avenues for the development of more precise and less invasive cancer treatments, ultimately enhancing patient outcomes in the clinical setting.

2.6. Challenges with AuNPs in Cancer Therapy

Despite their potential for cancer therapy, there are several challenges that need to be addressed before their widespread clinical application. The toxicity of AuNPs is one of the major challenges, and in vivo studies have shown that AuNPs can accumulate in organs such as the liver, kidney, and spleen, leading to toxicity.[154] AuNPs can also aggregate in biological fluids, which can alter their properties and therapeutic efficacy.[155] Therefore, ensuring the stability of AuNPs in physiological conditions is crucial for their effective use in cancer therapy. Additionally, the size, shape, surface charge, and surface coating of AuNPs can influence their toxicity.[156] Another challenge is the lack of specificity of AuNPs towards cancer cells, even when functionalized with targeting moieties such as antibodies or peptides. This lack of specificity is

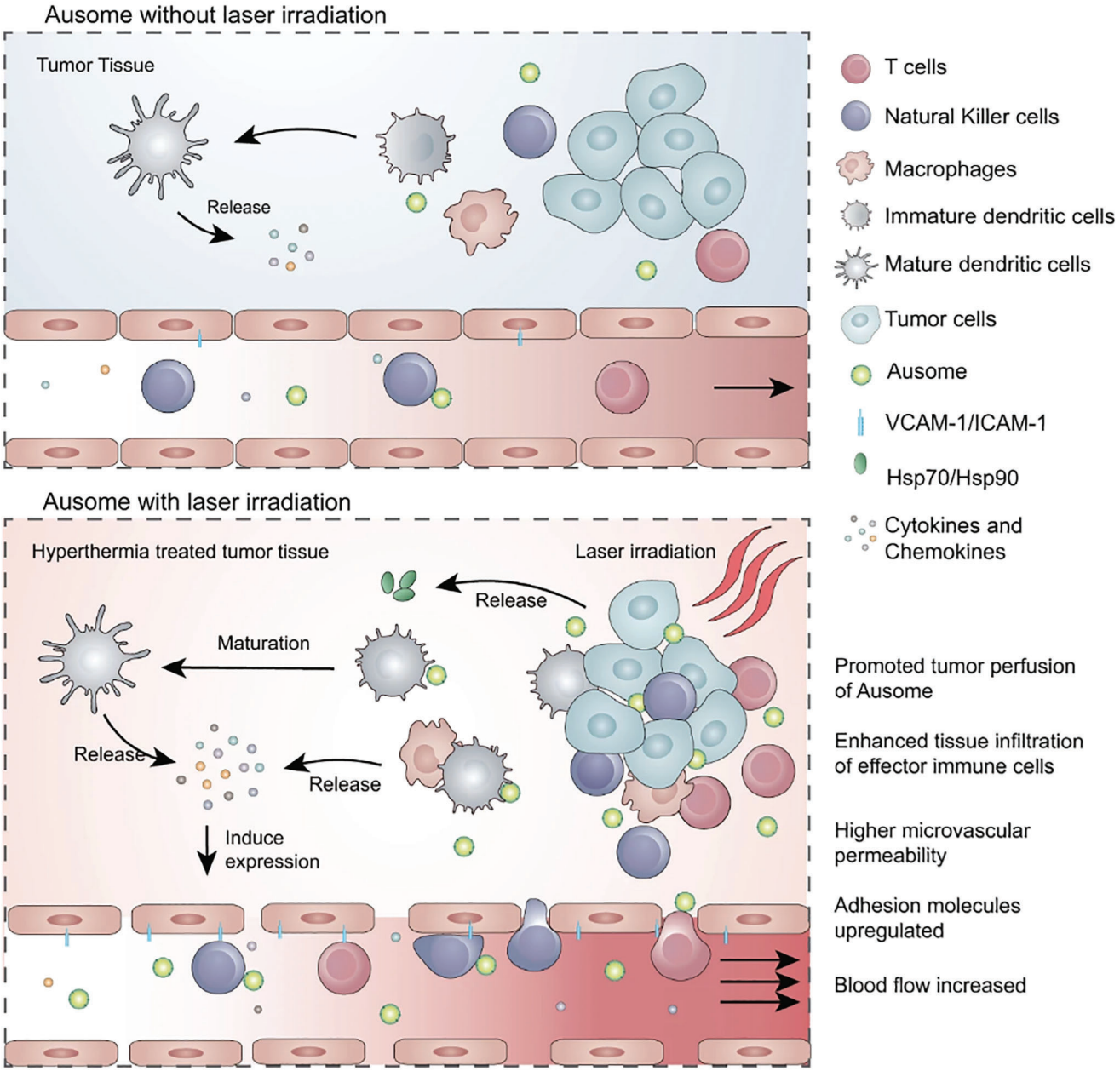

Figure 6. Ausome consists of a gold nanoparticle core surrounded by a bacterial component shell. Upon intravenous injection, it triggers a systemic immune response through microorganism-derived danger signals, activating immune cells and releasing pro-inflammatory cytokines. After tumor accumulation, laser irradiation induces mild hyperthermia, enhancing blood flow and vascular permeability, which promotes the infiltration of immune cells into the tumor. This targeted immune modulation amplifies immune responses within the tumor microenvironment while avoiding the side effects associated with high systemic doses of immunomodulators.[3] Copyright Nature Communications 2023. We are adapting under CC BY license by Springer Nature.

due to the heterogeneity of cancer cells and the complexity of the TME.[157] Moreover, AuNPs can induce immune responses that limit their therapeutic efficacy by being recognized as foreign particles by the immune system.[158] Therefore, strategies are needed to evade the immune system and enhance the circulation and accumulation of AuNPs in tumors. Furthermore, the production and characterization of AuNPs with consistent quality and properties are critical for their clinical translation. The variability in the synthesis and characterization of AuNPs can lead to differences in their physicochemical properties, affecting their toxicity and therapeutic efficacy.[154] Additionally, the synthesis of AuNPs needs to be scalable and reproducible for their clinical application. However, controlling the size, shape, and surface properties of AuNPs in a reproducible manner is challenging. Another challenge is the risk of resistance to AuNP-based therapies, similar to conventional chemotherapy. Understanding the mechanisms

of resistance and developing strategies to overcome it is a significant challenge. Lastly, the approval of AuNP-based therapies for clinical use involves rigorous testing and regulatory scrutiny involving extensive safety evaluations and regulatory approval. Recent clinical trials have started assessing the safety profiles of AuNPs, and studies have demonstrated their potential as therapeutic agents.[159] Despite these promising results, optimizing in vivo stability, ensuring efficient cellular uptake, and navigating complex biological barriers are ongoing areas of research to ensure the safety and efficacy of AuNPs-based drug delivery systems in clinical practice.[160] Strategies to overcome these challenges include optimizing nanoparticle properties, improving biodistribution and targeting efficiency, and conducting rigorous preclinical and clinical evaluations.

3. Silver Nanoparticles

3.1. Physicochemical Properties

AgNPs have unique physicochemical properties, including a high surface area-to-volume ratio, which enables efficient interaction with biological systems, such as cancer cells, enhancing their therapeutic and diagnostic potential in biomedical applications.[161] AgNPs also possess the ability to exhibit SPR. AgNPs exhibit strong surface plasmon resonance (SPR) within the 350–500 nm wavelength range, with maximal SPR typically observed around 410 nm. This unique optical property can be utilized in diagnostic techniques like surface-enhanced Raman scattering (SERS) and photothermal therapy (PTT). The ability of AgNPs to absorb light in both the visible and near-infrared (NIR) regions of the electromagnetic spectrum enables efficient conversion of light into heat, making them ideal candidates for PTT. By selectively heating cancer cells, PTT induces apoptosis while minimizing damage to surrounding healthy tissues.[162,163]

AgNPs are known for their strong antimicrobial properties, attributed to the release of silver ions that disrupt microbial cell membranes and inhibit growth. This characteristic is valuable in cancer therapy, as it can help prevent secondary infections and ensure sterility in diagnostic procedures. Additionally, the high surface energy and surface-to-volume ratio of AgNPs enable easy functionalization with biomolecules such as antibodies, peptides, and nucleic acids. This allows for targeted delivery of chemotherapeutic agents, minimizing toxicity to healthy cells. AgNPs have also been utilized to bind specifically to tumor biomarkers, aiding cancer diagnosis.[164,165] AgNPs can be synthesized using biocompatible materials and be functionalized with surface coatings, which reduce their toxicity and enhance their stability in biological environments. Additionally, their small size facilitates cell uptake, allowing for efficient delivery of therapeutic payloads.[165,166]

AgNPs can be employed as contrast agents in various imaging systems, such as CT, MRI, and optical imaging. Their strong scattering and absorption properties make them excellent candidates for improving the sensitivity and resolution of diagnostic imaging techniques.[161] The UV absorption properties of AgNPs also reveal that AgNPs can serve as contrast agents for PAI by absorbing NIR light and emitting acoustic signals, allowing for real-time visualization and characterization of tumor tissues.[167] Additionally, AgNPs enhance the sensitivity and specificity of Raman spectroscopy-based imaging methods through SERS, enabling label-free detection and molecular profiling of cancer biomarkers in biological samples.[168] The distinctive physicochemical characteristics of AgNPs make them very promising for cancer therapy, diagnostics, and theranostics. Their multifunctionality may be effectively used for precise disease diagnosis and targeted treatment.[161]

3.2. Synthesis Methods

Different methodologies have been reported to produce AgNPs in physical, chemical, and biological ways (**Figure 7**). AgNPs are commonly synthesized through the chemical reduction method, where silver ions (Ag^+) are reduced in solution by a reducing agent, such as sodium borohydride ($NaBH_4$), sodium citrate, or other organic compounds, to form nanoparticles. This approach offers precise control over the size and shape of AgNPs by adjusting key reaction parameters, including temperature, pH, and reactant concentrations. AgNPs can also be synthesized through green methods, which utilize natural sources such as plant extracts and biopolymers as eco-friendly reducing agents, offering a sustainable alternative to conventional chemical approaches. Unlike traditional methods that involve toxic chemicals, green synthesis for AgNPs leverages the reducing and stabilizing properties of phytochemicals, such as flavonoids, saponins, and terpenoids, found in various plant extracts. For instance, the leaf extract of *Eugenia jambolana* and the bark extract of *Saraca asoca* have been shown to contain these compounds, making them effective in the production of AgNPs.[169] Biopolymers such as carboxymethylated-curdlan or fucoidan have also been utilized as reducing and stabilizing agents, which yielded AgNPs with an appreciable particle size of 40–80 nm. Microbes such as bacteria, fungi, and algae can also be employed for synthesizing AgNPs through the reduction of silver ions present in the growth medium. Microbial synthesis offers scalability, cost-effectiveness, and ease of handling. Moreover, microbial synthesis produces nanoparticles with narrow size distributions and good stability. *Bacillus* sp. has been tested for the synthesis of AgNPs and has yielded great results with a particle size of 5–15 nm with a spherical structure. *Fusarium oxysporum* has also yielded a similar particle size. Many other microbes can yield AgNPs of the desired size, shape, and morphology.[170]

Photochemical methods offer precise control over the size, shape, and surface properties of AgNPs by utilizing light energy to reduce silver ions in the presence of a metal precursor. The synthesis process also involves the use of stabilizers and capping agents, such as synthetic polymers like polyvinylpyrrolidone (PVP) and polymethacrylate (PMA), or biopolymers like chitosan and gelatin, which prevent agglomeration and ensure uniform nanoparticle formation. These components are crucial in achieving AgNPs with the desired size and stability, making photochemical methods particularly effective for producing nanoparticles for biomedical applications. The method allows fine-tuning of AgNPs properties, with factors like pH playing a significant role. In alkaline conditions, higher pH accelerates the reactivity of the silver precursor, leading to smaller particle sizes, and also influences light absorption by the Ag precursor in solution. The choice of reducing and capping agents further affects

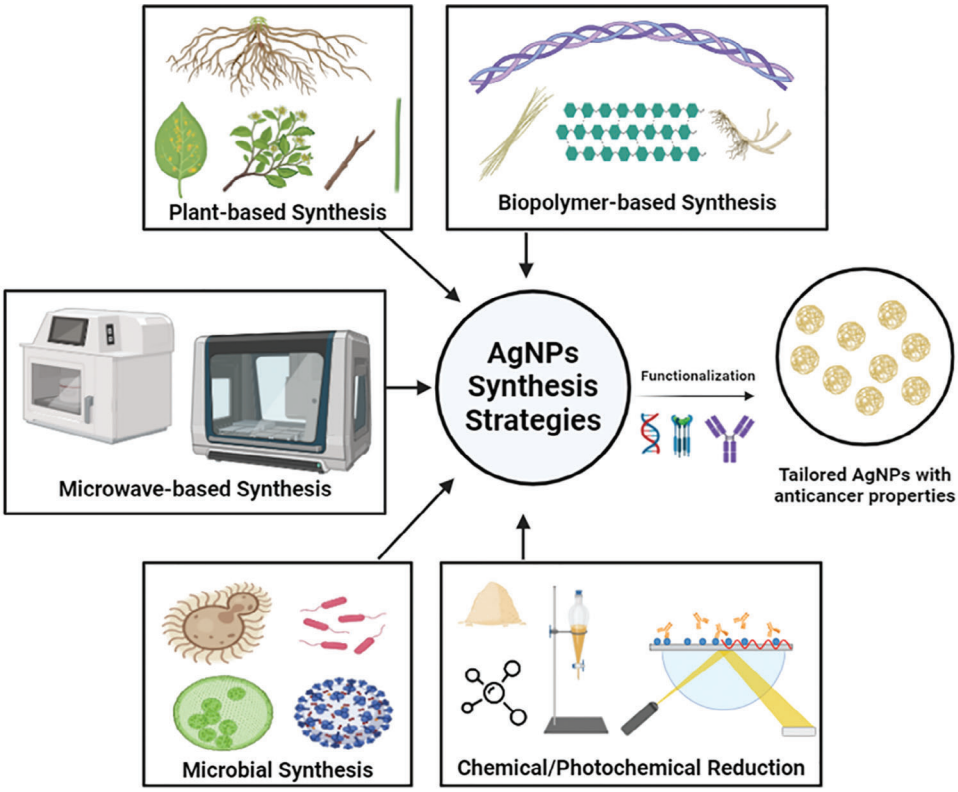

Figure 7. Overview of various strategies for synthesizing AgNPs with anticancer properties. These methods include plant-based synthesis, biopolymer-based synthesis, microwave-assisted synthesis, microbial synthesis, and chemical/photochemical reduction. Functionalization of AgNPs with biomolecules such as DNA, aptamers, and antibodies tailors their properties for enhanced anticancer activity.AgNPs with anticancer properties.

the structural characteristics of AgNPs, enhancing their potential in targeted drug delivery and diagnostic applications.[171] Some studies have also demonstrated that AgNPs can be photodynamically synthesized without the addition of a reducing agent. Microwave irradiation can be used to aid in the reduction of silver ions and the formation of nanoparticles in a very short time. Microwave-assisted synthesis offers rapid reaction kinetics, high yields, and improved reproducibility compared to conventional heating methods. This method is particularly useful for large-scale production of AgNPs. Another undeniable advantage of this method is that it produces negligible chemical waste. Microwave synthesis does involve reagents other than the Ag precursor in solution to carry out the reduction process and for stabilization. The solution is generally an aqueous medium, but other solvents, such as benzophenone, have also been examined. Usually, polymeric materials such as carboxymethyl cellulose (CMC) or PVP are employed as reducing agents in this type of synthesis. Some reports claim to have achieved a particle size of 12 nm through microwave synthesis. Microwave synthesis proves to be a much greener way of synthesis compared to other methods.[172]

There have also been reports of using polymeric entities like dendrimers to assist in the synthesis of AgNPs, primarily to control nanoparticle size. However, this method alone is not very efficient without the aid of additional reducing agents. A promising approach involves the metal transfer strategy, where CuNPs coated on dendrimers are oxidized in the presence of an Ag precursor, yielding AgNPs. While this technique has produced AgNPs as small as 2.8 nm, a challenge remains in completely removing residual metal ions from the dendrimer matrix.[173] Another interesting strategy that can be used to obtain AgNPs of desired shapes is fractal assemblies using peptides, which essentially control the nucleation of AgNPs. This could particularly be relevant when AgNPs are applied for disease detection using various biomarkers.[174] Likewise, DNA origami also can be used to guide the self-assembly of AgNPs. This strategy has also yielded a particle size under 20 nm.[175] Apart from these methods to obtain AgNPs, there is a definitive need to functionalize with a capping agent that can prevent the formation of a protein corona around these nanostructures. These capping agents are generally silica and zinc sulfide. Small functional head groups such as amine, phosphine, or thiol groups can also serve the purpose, using electrostatic interactions. This can lead to clumping of the AgNPs. However, PEG resolves the problem, as it can increase hydrophilicity (an important aspect for clearance) and prevent corona formation. These stabilized AgNPs can be further functionalized or bio-conjugated with targeting ligands. AgNPs can be functionalized for cancer therapy by targeting ligands or anticancer drugs to specifically target cancer cells in a chemodynamic or photodynamic way of minimizing damage to adjacent healthy cells. Surface functionalization can be done using covalent and non-covalent approaches. The strategies include the addition of a thiol, amide, imide, or other small subunits that can be attached to a targeting moiety such as DNA, antibodies, or other proteins using covalent, electrostatic, or hydrophobic in-

teractions. Nanoparticles are generally functionalized with anticancer drugs for cancer therapy; AgNPs can also be used in the same manner due to their commendable surface area-to-volume ratio. Some methods also adopt functionalization with antimicrobial drugs to prevent secondary tumor site infections.

3.3. Therapeutic Applications in Cancer

AgNPs have demonstrated excellent antibacterial activity through several mechanisms. They can directly interact with bacterial cell membranes, with Ag^+ ions disrupting the cell wall and entering the cell to denature ribosomes and inhibit ATP production, which is crucial for bacterial growth. Additionally, AgNPs generate reactive oxygen species (ROS), further aiding in cell wall disruption. AgNPs also interfere with DNA replication by disrupting the affinity between sulfur and phosphorus in DNA, affecting bacterial reproduction. They exhibit broad-spectrum activity against both Gram-positive and Gram-negative bacteria, with specific mechanisms varying by pathogen.[176] For example, in *Enterococcus faecalis*, *Acinetobacter baumannii*, and *Proteus mirabilis*, AgNPs disrupt the cell wall, while in *Staphylococcus epidermidis* and *Salmonella typhi*, they inhibit DNA replication and reduce ATP production. In other cases, such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Vibrio cholerae*, AgNPs disrupt respiration, leading to bacterial lysis. The antibacterial efficacy of AgNPs is influenced by their size, shape, and morphology, with smaller, porous structures showing better activity.[177] This broad-spectrum antibacterial activity is particularly valuable in medical applications such as wound dressings and coatings for medical devices, and it is also beneficial in cancer therapy by preventing infections during treatment and reducing reliance on antibiotics, potentially minimizing the risk of developing antibiotic resistance.[178]

AgNPs have shown significant potential in antiviral applications by inhibiting viral attachment, entry, replication, and release. They exhibit activity against various viruses, such as influenza, HIV, herpes simplex virus, and hepatitis B virus. For example, AgNPs coated with polyvinylpyrrolidone (PVP) were used to treat HIV-1 by interacting with the gp120 protein, essential for viral attachment to CD4 T-cells. By disrupting gp120, AgNPs hinder the virus from penetrating host cells. Similarly, AgNPs demonstrated antiviral activity against respiratory syncytial virus by interfering with viral attachment to host cells.[179,180] AgNPs also exhibit other antiviral mechanisms, such as binding to cysteine residues, inactivating viral DNA, and inhibiting viral replication and membrane binding. The most effective antiviral activity is typically observed with particles less than 10 nm in size due to their increased mobility and ability to interact with viral structures. AgNPs hold promise for developing antiviral coatings for surfaces, personal protective equipment, and medical devices, potentially helping to prevent the spread of viral infections, including emerging and drug-resistant strains.[181,182] In the context of cancer, their antiviral properties could be beneficial in reducing viral-related infections and complications during cancer treatment, enhancing patient outcomes, and minimizing treatment disruptions.

AgNPs show potential as versatile agents for targeted delivery of drugs, PTT, and radio sensitization in the arena of cancer therapy. Due to their ability to specifically target cancer cells without damaging healthy cells, they are highly suitable for cancer treatments. As discussed earlier, AgNPs may be modified with targeting ligands or anticancer chemotherapeutic drugs to improve their selectivity and effectiveness against malignant tumors. In vitro tests have shown that AgNPs can trigger apoptosis by producing free oxygen radicals exhibiting antitumor, antiproliferative, and antiangiogenic properties.[183] Furthermore, it has been found that AgNPs disrupt the regular functioning of cells and affect the integrity of cell membranes by activating various genes associated with programmed cell death in mammalian cells, ultimately leading to cell death.[184] The generation of high levels of ROS is widely recognized to cause cellular damage by damaging the mitochondrial membrane, leading to toxicity. Studies show that AgNPs can trigger programmed cell death through apoptosis even when the p53 tumor suppressor is absent. Further evidence that the cytotoxic effects of silver and hybrid AgNPs are cell-type specific suggests that these substances may have different effects on different types of cells.[185] The formation of ROS and the resulting damage caused by oxidative stress depend on the size of AgNPs. Smaller AgNPs lead to a more significant overproduction of ROS. AgNPs can disrupt the mitochondrial chain and complex, contaminating superoxide anions.[186] In this context, the released Ag+ ions, affect the activity of mitochondrial enzymes and interact with the –SH groups of proteins and glutathione. As a result, the ability of glutathione to scavenge ROS declines, leading to oxidative stress. Genetic material may also undergo alterations that lead to changes in how genes are expressed. As a result, cancer cells may undergo apoptosis.[187] These mechanisms enable AgNPs to be employed for anticancer applications, offering precise control over their therapeutic effects.

3.4. Targeted Drug Delivery for Cancer

AgNPs can be passively targeted to tumor cells by leveraging the EPR effect or through surface functionalization and bioconjugation, leading to their accumulation at the tumor site and enabling anticancer activity (**Figure 8**). The size and concentration of AgNPs administered play a critical role in determining the extent of accumulation.[188] While passive targeting has shown promise in xenograft models with well-developed tumors, clinical translation in actual tumors has not yielded similar results. Therefore, it is essential to explore alternative active targeting strategies that may offer better clinical outcomes.[189] In exploring active targeting, generally, a cancer cell-specific ligand such as an antibody or a cell-penetrating peptide (CPP) is attached to the surface of the nanoparticle to enhance the ingestion of AgNPs by the targeted cell population.[190] CPPs are short, positively charged peptides predominantly composed of arginine and lysine. They can transport themselves and their associated substances across the tumor cell's plasma membrane.[191] Soybean agglutinin exhibits a selective affinity for cancer cell membrane patterns, making it an attractive targeting approach for this category of cancer cells. It was discovered that AgNPs conjugated with soybean agglutinin were specifically harmful to breast cancer cell lines (MDA-MB-231 and MCF-7) but did not harm noncancerous breast epithelial cells (MCF-10A). Likewise, different polymers or antibodies could target different cancer cell types.[192]

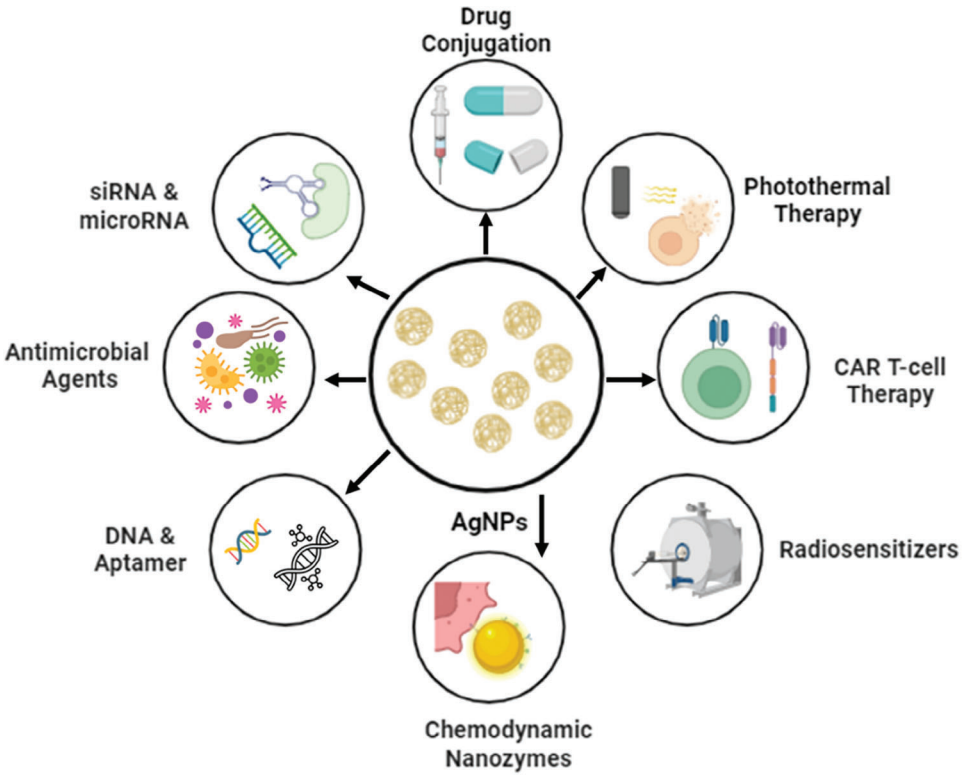

Figure 8. Cancer cell targeting strategies using AgNPs. This diagram illustrates the various approaches for targeting cancer cells with AgNPs, including passive targeting via the EPR effect, increased circulation, and active targeting through receptor-mediated endocytosis. AgNPs can also be functionalized with ligands for specific binding to cancer cell surface receptors, improving bioavailability and therapeutic efficacy.

AgNPs have also been conjugated with folic acid to target the folate receptors in a cancer cell.[193] In another study, the drug MTX had been loaded onto the surface of AgNPs-graphene oxide nanocomposite to target the same receptors.[194] The acidic nature of the TME also facilitates the release of Ag+ ions and enables its therapeutic activity.[195] Another key factor to be considered when engineering AgNPs-based therapeutic systems is the formation of protein corona on the surface of AgNPs, which can impact the therapeutic efficiency of these systems. Protein corona formation tends to alter the engineered nanomaterial's physical properties, thereby influencing interactions with bodily fluids.[196]

AgNPs are taken by the TME and interact with the tumor stroma, which includes leaky blood vessels and plasma proteins, among other cellular and non-cellular components. Silver-coated AuNPs can interfere with the interaction between cancer-associated fibroblasts and carcinoma cells, reducing metastatic activity in cancer cells in vivo.[197] Another study suggested that cell migration and production of laminin-1 and collagen-1 (cancer biomarkers) were reduced in fibroblasts treated with AgNPs, further demonstrating the potent inhibitory effects of AgNPs on stromal fibroblasts.[198] AgNPs of different sizes enhance the expression of IL-1b and IL-8 messenger RNA (mRNA) levels and stimulate the generation of ROS in macrophages.[199] This trend is also observed in the recent study where AgNPs served as a multifunctional drug delivery system alongside the chemotherapeutic DOX, which has been proven to inhibit tumor-associated macrophages.[200] The non-cellular components of the TME can also affect the ability of AgNPs to penetrate tumor tissues and cells, as well as specific events that occur within these cells. The rigidity of the ECM determines the process of metastasis and may also impact the distribution of AgNPs within a tumor. Significantly, AgNPs have been demonstrated to inhibit the release of extracellular fluids, and they can affect the function of cells that produce the matrix in the TME.[201] Moreover, a study has demonstrated that AgNPs of size 20 nm enhance the secretion of MMP-9 and, as a result, the gelatinase activity of neutrophil cells. This suggests that AgNPs circulating in the TME have the potential to influence the composition of the ECM effectively.[201] The mechanism by which tumor cells internalize the circulating AgNPs has also been studied to decipher an optimal strategy to deliver these nanostructures. Usually, AgNPs are internalized by endocytosis; however, in some cases, the endocytosis pathways are impaired, resulting in reliance on other uptake mechanisms.[202] Another study also proved that the polymer or surfactant material used to coat AgNPs impacts the uptake of AgNPs in cells.[203] PEGylation can alter the surface charge of AgNPs, minimizing its cytotoxicity and opening an array of drug delivery approaches.[204]

Upon uptake through different pathways in different types of tumors, AgNPs interact with various intracellular pathways depending on the type of cancer cell. The acidic nature of the TME results in the release of Ag+ ions, which alters intracellular pathways.[205] The introduction of AgNPs into a cell leads to ROS generation, ultimately causing apoptosis. However, there is no

selectivity, as these ions can also lead to apoptosis of adjacent normal tissues.[206] AgNPs have also been found to trigger autophagy in prostate cancer cells.[207] AgNPs show great potential as carriers for drug delivery, especially in the field of anticancer therapy. Their utility can be attributed to their capacity to be functionalized with targeted ligands, using the EPR effect and reacting to the acidic TME. AgNPs have demonstrated significant potential as effective agents against tumors. Significantly low amounts of AgNPs can lead to DNA damage and chromosomal abnormalities without causing major cytotoxicity. AgNPs have demonstrated anticancer properties through different mechanisms. In some cases, AgNPs inhibit the formation of new blood vessels across the tumor tissue, resulting in a lack of nutrition, ultimately leading to lysis. Against MDA-MB-231 human breast cancer cells, AgNPs have altered the cell viability and induced membrane leakage to establish anticancer activity.[207] AgNPs have also altered the mitochondrial function in human lung cancer A549 cells to achieve apoptosis.

Various chemotherapeutic drugs have been combined with AgNPs systems to provide controlled and precise drug release to the tumor tissue. The simultaneous exposure of cell lines to a combination of AgNPs-Cisplatin resulted in cytotoxicity and oxidative stress. However, this combination was particularly effective in targeting and killing tumor cells. The proteome analysis revealed increased energy metabolism pathways, decreased cell cycle regulators, and distinct reactions to oxidative stress in normal and tumor cells.[208] AgNPs-polyethyleneimine complex loaded with PTX exhibited a significant cytotoxic impact on HepG2 cells, leading to increased susceptibility to drugs and the initiation of programmed cell death, specifically in cancer cells, compared to normal cells.[209] AgNPs-polymeric nanocrystals loaded with the chemotherapeutic DOX had a synergistic cytotoxic effect on MCF-7 cells at significantly lower dosages while having a lesser cytotoxic effect on normal 1BR hTERT cells.[210] Thus, AgNPs show a lot of potential in anticancer therapy. Apart from the therapeutic effectiveness of AgNPs against cancer, AgNPs also show promise in cancer diagnostics, biosensing, or radio sensitizing, which can again be attributed to their surface properties. An interesting study revealed that the radio sensitization of AgNPs to treat glioma can be enhanced by introducing a surface modification using an aptamer As1411; likewise, the tunable surface can be exploited to target other cancer types.[211] The potential of AgNPs to eliminate cancer cells via PTT is also being investigated. AgNPs convert near-infrared light into thermal energy, thereby eradicating cancer cells through localized hyperthermia. PTT is promising because of its possible synergy with other therapies.[212] AgNPs are also being explored in the field of cancer biosensing. Scientists can develop exceptionally sensitive detectors for cancer-associated biomarkers by serving as signal enhancers. By affixing targeting molecules to AgNPs, these biosensors surpass the capabilities of conventional methods in terms of cancer detection time and accuracy. Employing monitoring may ultimately result in more precise diagnoses, enhanced treatment decisions, and improved patient outcomes. Thus, AgNPs offer a lot of attractive properties and mechanisms that make them excellent candidates in cancer therapy, diagnostics, and theranostics.

3.5. Challenges with AgNPs in Cancer Therapy

Nanomaterials are extremely cytotoxic to mammalian cells due to their interaction with biomolecules that generate reactive oxygen via defense mechanisms that induce oxidative damage to lipids, proteins, and DNA. Nanotoxicity concerns regarding AgNPs are multifaceted and revolve around their unique physicochemical properties. Their small size and large surface area-to-volume ratio enable them to interact with biological systems at the cellular and molecular levels, potentially leading to adverse effects. The primary concern is the release of Ag+ ions which occurs under physiological conditions and contributes to the antimicrobial and anticancer activity of AgNPs. However, excessive Ag^+ release can induce oxidative stress by generating ROS, leading to lipid peroxidation, protein damage, and DNA strand breaks. This oxidative stress can disrupt cellular functions and activate inflammatory pathways, resulting in cytotoxicity and tissue damage. Surface modifications and coatings can be employed to enhance the stability and biocompatibility of AgNPs, reducing their cytotoxicity and improving their safety profile.[213] Comprehending how AgNPs are distributed and eliminated in living organisms is crucial for assessing their safety and effectiveness in cancer treatment. AgNPs can build up in different organs and tissues, leading to systemic toxicity and unintended effects in other body areas. Modulating the dimensions, morphology, and surface characteristics of AgNPs can impact their dispersion throughout the body and the rate at which they are eliminated. Additionally, creating biodegradable AgNPs formulations can aid in better metabolism and removal from the body, decreasing the potential for long-term buildup and systemic toxicity. AgNPs have the potential to induce immunological responses and inflammatory reactions in living organisms, which can result in concerns over their ability to provoke an immune response and cause toxicity to the immune system. The interaction between AgNPs and immune cells can impact the activation and functioning of the immune cells, as well as the production of cytokines. Methods for reducing immunotoxicity involve assessing the immunological impacts of AgNPs in preclinical animals and refining nanoparticle compositions to decrease immune reactions. In addition, including immunomodulatory drugs or biocompatible coatings can assist in regulating immune responses and enhancing the safety of AgNPs in cancer treatment.

Research indicates that following systemic, oral, or nasal treatment, AgNPs accumulate in several organs, including the liver, kidney, spleen, lungs, heart, and testis. Significant changes in the structure of tissues, disruptions in metabolic processes, and damage to genes and the immune system were observed in several soft tissues following the injection of AgNPs, whether for a short or extended time. The precise mechanism by which AgNPs accumulation affects the functioning of the soft tissues and organs remains unclear. However, a substantial quantity of AgNPs accumulated in the malignant tissue of mice with solid tumors injected intravenously with radiolabeled AgNPs, deciphering the tissue selectivity abiding by pH conditions. Ignoring the negligible nanoparticle buildup in the liver and spleen of the animals, a significant concentration of AgNPs specifically accumulating in tumor cells demonstrates that intravenously delivered

AgNPs can effectively target malignant tissue over adjacent healthy tissues.[214] PEGylation has been presented as an alternate method to enhance the stability of silver quantum dots in plasma and decrease their toxicity to the liver. Dextran-coated AgNPs can avoid recognition and clearance by reticuloendothelial system cells. Additionally, they exhibited an extended duration in the bloodstream and reduced accumulation in the spleen following systemic treatment, compared to non-coated AgNPs.[215] Thus, the safety aspects of these nanostructures can be ensured by employing biocompatible polymeric coatings that ensure in vivo stability and do not affect the therapeutic function of AgNPs.

Small interfering RNA (siRNA) and microRNA (miRNA) are two examples of nucleic acid-based therapeutics that can be delivered by attachment to the surface of AgNPs. These therapies target specific genes that are implicated in the progression of cancer. The simultaneous manipulation of several important signaling pathways in the development and progression of cancer is made possible with the combination of gene therapy and AgNPs. Synergistic antitumor effects can be achieved without causing drug resistance in cancer cells using AgNPs functionalized with siRNA targeting oncogenes and chemotherapeutic drugs. This allows for the simultaneous treatment of cancer cells by AgNPs, siRNA, and drug molecules. siRNA interference has shown significant therapeutic potential due to its high specificity and capacity to potentially overcome antimicrobial drug resistance in vivo in an AgNPs-based drug delivery system.[216] AgNPs can enhance the efficacy of immunotherapies, such as immune checkpoint inhibitors or chimeric antigen receptor (CAR) T-cell therapy. AgNPs can serve as carriers for immunomodulatory drugs, cytokines, or tumor-associated antigens. This enables the activation of immune cells and the identification of malignancies. Combining AgNPs with immunotherapies can potentially stimulate anticancer immune responses. Additionally, this can augment the infiltration of immune cells into tumors and optimize the efficacy of cancer immunotherapy methods.[217] AgNPs can function as photosensitizers in photodynamic therapy, a non-invasive treatment method that employs light-activated photosensitizers to produce ROS and cause the death of cancer cells. Combining AgNPs with photodynamic therapy increases the absorption of light and the formation of ROS, resulting in enhanced destruction of tumors and less harm to nearby healthy tissues. Furthermore, AgNPs can be linked with targeting ligands to specifically transport photosensitizers to cancerous cells, improving the precision and effectiveness of treatment. This property can also be explored to improve diagnostic standards.

AgNPs can also make cancer cells more sensitive to ionizing radiation, improving the efficacy of radiotherapy. By introducing AgNPs into tumor tissues, the harmful effects of radiation on DNA and cell survival can be enhanced by generating secondary electrons and ROS. Using a combination of AgNPs with radiotherapy also provides a synergistic method for overcoming resistance to radiation and enhancing the effectiveness of tumor treatment for different forms of cancer.[211] As discussed earlier, AgNPs can be conjugated with tumor-targeting ligands, such as antibodies or peptides, to selectively deliver chemotherapeutic drugs or other therapeutic agents to cancer cells. Combining AgNPs with targeted drug delivery systems allows precise drug delivery to tumor tissues while minimizing systemic toxicity and off-target effects. This approach enhances therapeutic efficacy, reduces treatment-associated side effects, and improves patient outcomes in cancer therapy. Aside from regular AgNPs, Silver enzymes offer a potential frontier in cancer therapy due to their intrinsic enzymatic activity. Nanozymes imitate the catalytic characteristics of natural enzymes, providing benefits such as improved stability, reduced expenses, and streamlined production methods. The enzymatic activity of silver nanozymes has considerable potential in cancer treatment. Their capacity to scavenge ROS can alleviate oxidative stress, a characteristic feature of cancer cells, impeding cancer advancement and spread. In addition, silver nanozymes can be employed in PTT, where their catalytic activity effectively transforms light into heat, allowing for targeted destruction of tumor tissues while limiting harm to adjacent healthy cells. Furthermore, the enzymatic characteristics of silver nanozymes can augment the efficacy of chemotherapy by facilitating the intracellular transportation and release of drugs through the breakdown of cancer cell membranes and organelles. In addition, these nanozymes can function as adaptable biosensors for identifying cancer biomarkers or as imaging agents for seeing tumor tissues. Their catalytic activity can be explored to achieve accurate tumor targeting and sensitive tumor detection. Researchers could employ the enzymatic activity of silver nanozymes to create advanced nanomedicine platforms for targeted cancer therapy.

3.6. Toxicity and Safety

The potential toxicity and safety of AgNPs are currently being extensively studied and investigated in a range of biomedical applications, particularly in the field of cancer therapy. Although AgNPs show promise as a therapeutic option, it is crucial to thoroughly assess and minimize any potential negative impacts they may have on human health and the environment. Various studies and publications imply that AgNPs can harm both humans and the environment. Industrial waste releases large quantities of silver into the environment, leading to environmental toxicity. Free Ag+ ions harm humans and all living organisms, including developing a permanent bluish-grey discoloration of the skin (argyria) or the eyes (argyrosis). Exposure to soluble silver compounds can also result in toxic effects such as liver and kidney damage, irritations of the eyes, skin, respiratory system, and intestinal tract, and undesirable alterations in blood cells. Research indicates that AgNPs cannot distinguish between dangerous and beneficial bacteria in the environment. There has been minimal research conducted to assess the toxicity of AgNPs. The in vitro toxicity experiment of AgNPs indicated that low-level exposure to these nanoparticles induces oxidative stress and impairs mitochondrial activity in rat liver cells. AgNPs exhibited toxicity to mouse germline stem cells in vitro by disrupting mitochondrial activity and inducing cell membrane leakage. They harm sperm cells in the male reproductive system by crossing the blood–testis barrier and accumulating in the testes. The liver is the specific organ in mice that is targeted by AgNPs, as demonstrated by in vivo experiments examining the oral toxicity of rats. The increased prevalence of bile duct hyperplasia, with or without necrosis, fibrosis, and pigmentation in the in vivo studies, indicates that the release of silver occurs when nanoparticles are held for an extended duration. This suggests that exposure to AgNPs for a

long, continuous period is more harmful than minimal exposure time.[218]

Depending on the dosage, AgNPs may trigger cell death and negatively affect cellular activities. The cytotoxicity of AgNPs is mediated by ROS-dependent pathways, DNA damage, mitochondrial dysfunction, and inflammation. Furthermore, AgNPs can interact with cellular membranes and organelles, causing abnormalities in regular cellular functions and triggering apoptosis or necrosis. The cytotoxicity of AgNPs is influenced by parameters such as their size, shape, surface chemistry, and exposure time. An interesting study illustrates that the impact of AgNPs-based toxicity can vary concerning the physical interactions between AgNPs and the cell membranes of the exposed cells, which in turn depends on the surface charge of the AgNPs and the membranes.[219] Another study illustrates the potential genotoxicity and impact on apoptosis regulating the p53 oncogene by AgNPs, from which AgNPs are highly selective, and thus, no trend is observed even in similar types of cells. Thus, any cell with which the AgNPs may interact must be tested in vivo before application.[220] Orally administered AgNPs of size 10 nm displayed oxidative stress in the brain but not the liver of Wistar male rats.[221] When the particle size increases to 20 nm, AgNPs induce oxidative stress to the liver and the heart in vivo.[222] Further increases in particle size lead to the accumulation of silver in the kidneys, with a higher accumulation in females, illustrating the potential nephrotoxicity of AgNPs.[223] However, another study suggests no toxicity was observed in the blood or any organs when exposed to AgNPs of size up to 110 nm.[224] The presence of significant quantities of AgNPs has detrimental effects on the kidney function's physiological, biochemical, and histopathological aspects in *C. gariepinus*, further illustrating the nephrotoxicity claim.[225] AgNPs have also been proven to induce autophagy in cells, which can lead to neurodegenerative diseases such as Alzheimer's or Parkinson's. Another study found that AgNPs with a size range of 3–5 nm can penetrate mouse brain cells and cause the production of proinflammatory cytokines. Additionally, these nanoparticles can promote the deposition of Aβ amyloid in response to changes in gene expression related to inflammatory response, oxidative stress, and Aβ breakdown, indicating that the neuroinflammatory response caused by AgNPs could contribute to the development of neurodegenerative diseases.[226] Intentionally or unintentionally introducing AgNPs into the environment can harm ecosystems and human well-being. Additionally, AgNPs have the potential to undergo changes and engage with environmental elements, which might modify their toxicity and availability in biological systems. Methods for reducing the amount of environmental exposure to AgNPs encompass wastewater treatment, recycling, and appropriate disposal procedures. Thus, all such aspects must be considered when developing AgNP-based cancer therapies.[227]

4. Iron Oxide Nanoparticles (IONPs)

IONPs, particularly SPIONs, possess inherent magnetic properties that make them highly suitable for biomedical applications. Their small size, biocompatibility, and tunable surface chemistry allow for precise control over their behavior in biological systems, making them ideal candidates for cancer treatment. One of the most promising applications of IONPs in cancer therapy is targeted drug delivery. Functionalizing the surface of IONPs by targeting ligands such as antibodies or peptides can selectively deliver therapeutic agents to tumor sites while minimizing systemic toxicity. This targeted approach enhances the efficacy of anticancer drugs and reduces side effects associated with conventional chemotherapy. In addition to targeted drug delivery, IONPs can be utilized in hyperthermia therapy for cancer treatment. When exposed to an AMF, SPIONs generate heat through magnetic relaxation, leading to localized hyperthermia within tumor tissues. This hyperthermia selectively damages cancer cells while sparing surrounding healthy tissues, offering a minimally invasive approach to treating solid tumors. Furthermore, IONPs prove efficacious as contrast agents across diverse imaging modalities, including MRI. Their magnetic properties enhance the visualization of tumors and metastases, allowing for accurate diagnosis, staging, and treatment monitoring. Additionally, IONP-enhanced imaging enables real-time guidance during cancer interventions, facilitating precise targeting and delivery of therapeutic agents. The versatility of IONPs extends to theranostic applications, where they can serve dual roles as diagnostic imaging agents and therapeutic carriers. By combining imaging and therapy in a single nanoparticle platform, theranostic IONPs enable personalized treatment strategies, prognosis, and improved patient outcomes.

4.1. Magnetic Properties Relevant to Cancer

A thorough examination of the magnetic characteristics that influence the utility of IONPs in cancer theranostics. In 1957, Gilchrist et al. introduced the idea of utilizing magnetic iron oxide particles suspended in fluid for heating when exposed to AMF.[228] The interaction between magnetic fields and these particles predominantly produces heat through magnetic hysteresis loss.[229] In therapeutic applications, the area containing these nanoparticles is subjected to AMF. The heat generated, primarily through hysteresis heating driven by the interaction between the magnetic moments of the nanoparticles and the AMF, is then moved through the tissue by means of conduction and convection.[229] Magnetic nanoparticles produce heat by converting energy from an applied oscillating magnetic field via the field-driven moment, namely reversal and relaxation. Heat generation involves the magnetization vector following an irreversible trajectory around an energy barrier, known as anisotropy.[229–231] This process entails an associated transfer of magnetic energy through forced hysteresis losses. Therefore, the heat generation is directly proportional to the area enclosed by the hysteresis loop. The heating performance is typically quantified by specific loss power (SLP), expressed in units of W g^{-1} material, representing the amount of electromagnetic energy absorbed by the magnetic system and converted into heat.[232,233]

In contrast to ferromagnets, SPIONs possess a magnetism that can be externally manipulated. Due to their small size, smaller than that of a single magnetic domain (below 30 nm), their magnetic properties become evident only when an external magnetic field is present. This feature can be confirmed by performing a hysteresis loop, where the particle undergoes

exposure to increasing magnetic field strength until it achieves saturation in magnetization in two opposing directions.[234–236] Under an equivalent magnetic field strength, SPIONs exhibit significantly higher magnetization values than paramagnetic nanoparticles. However, their inherent magnetization is zero in the absence of an external magnetic force.[237] These attributes are crucial in medical applications where SPIONs' magnetism can be selectively activated for specific spatio-temporal windows during diagnosis and treatment.[238,239] The magnetic behavior of SPIONs is not solely dependent on their size; this could also be modulated by employing suitable additives or coatings.[240,241] These characteristics render SPIONs highly promising for theranostic applications, encompassing diagnostic imaging and therapeutic interventions for neoplastic diseases. Their ability to form stable colloidal systems in physiological environments enhances their potential as multifunctional tools in cancer theranostics.[236] Thus, these versatile properties of Fe_3O_4 SPIONs offer a wide array of potential applications.[242,243] For example, during PTT, they serve as cargo for agents that absorb NIR. Upon exposure to laser light, these agents emit heat, which can effectively eliminate cancer cells within a targeted area through tumor ablation induced by high temperatures.[244,245] In both scenarios, produced heat causes destruction to cancer cells, which are typically less tolerant to hyperthermia than healthy cells. When temperatures reach ≈42 °C, tumor cells can become more sensitive to other therapies, allowing for a reduction in the required dosage of radiation or medication and thereby mitigating the therapy's adverse effects.[246] Fe_3O_4 SPIONs also find successful applications in chemotherapy for drug delivery due to their facile functionalization, enabling them to serve as a platform for various therapeutic substances bonded to their surface. Utilizing SPIONs as nanocarriers prolongs the drug circulation time in the bloodstream, enhancing drug efficacy and facilitating controlled drug release depending on factors such as temperature, pH, or enzymes.[247] This approach helps to minimize the adverse effects on healthy cells. Tailoring of coating dynamics can enhance the adsorption of some molecules, such as paclitaxel, enabling targeted delivery to targeted areas.[248] Moreover, combining these NPs with liposomes allows the optimization of both targeted delivery and the release pattern. For instance, DOX, a commonly used cytostatic drug in cancer treatment, can be incorporated within lipid membranes alongside superparamagnetic nanoparticles. In addition to targeted drug delivery SPIONs also enable controlled release of DOX by applying an AMF, which can induce hyperthermia locally or physical disruption, leading to the destruction of liposomes.[249,251] However, excessively robust magnetism may lead to IONPs attracting one another, leading to aggregation and, thereby, potentially causing embolism in blood capillaries. Consequently, modifying IONPs to modulate the intensity of their magnetism is critical in ensuring their safe and effective application within the medical domain.

In conditions like cancer, where precise delivery is critical to optimize therapeutic effectiveness while minimizing off-target effects, magnetic guidance proves exceptionally advantageous. Attaining efficient targeting at specific sites may not be feasible solely through passive targeting using nanocarrier-based drugs reliant on the EPR effect. Studies have indicated that a mere fraction, approximately 0.7% (median), of nanoparticles can successfully reach solid tumors following systemic administration.[252] Given the superparamagnetic behavior of SPIONs, their responsiveness to external magnetic fields facilitates targeted delivery to specific anatomical sites within the body, thereby enhancing the accuracy of drug or gene delivery and ensuring elevated concentrations of therapeutic load at the intended location.[253] Furthermore, SPIONs have the distinctive ability to produce localized heat upon exposure to an AMF. Due to their single-domain characteristic, SPIONs can induce localized temperatures ranging from 45 to 47 °C through orientational thermal fluctuation, driven by either Brownian or Néel mechanisms in an external magnetic field.[254] This property endows SPIONs with significant value for advanced applications such as hyperthermia and PTT, offering targeted and localized treatment modalities for cancer therapy.

Apart from hyperthermia, the magnetic characteristics of ferumoxytol have led to the innovation of several approaches for tumor treatment. For instance, a recent study introduced a novel therapeutic approach called magneto-endosomalytic therapy (MELT), leveraging ferumoxytol's magnetic properties.[255] They observed that internalized ferumoxytol has the potential to be spontaneously ordered into certain morphology when subjected to parallel magnetic fields, resulting in the disruption of endosomes and initiation of apoptosis at cancerous tissue without affecting the benign cells/tissue. Ferumoxytol infiltrates tumor cells via endocytosis, and placing these cells between magnets creates a parallel magnetic field. As directed by the magnetic field, internalized ferumoxytol assembles into certain structures, leading to the destruction of endosomes and the deactivation of cancerous cells. Additionally, the therapeutic potential of MELT for solid tumors was assessed using a model of human prostate cancer. The findings illustrated that the binding of ferumoxytol to the small molecule ligand (DupA) targeting the prostate-specific membrane antigen substantially boosted the cellular uptake of ferumoxytol by tumor organoids. Introducing a magnetic field effectively decreased tumor cell survival rates and markedly reduced solid tumor volumes, indicating the significant therapeutic impact on cancer cells. MELT introduces a novel approach for utilizing ferumoxytol in cancer treatment. However, this study was confined to cultured cells and 3D organoids. Enhancing precision targeting can potentially be facilitated by employing a two-tier targeting combination strategy, which includes PMSA-directed molecular targeting alongside whole-body targeting utilizing parallel magnet placement. The precision and safety of MELT in live subjects require further exploration and confirmation.

4.2. Synthesis Techniques

The methodology used in synthesizing IONPs is essential as it can influence their physical and chemical properties, stability, movement, and efficiency in removing pollutants. Typically, IONPs synthesis employs either a bottom-up approach (where atoms and molecules are assembled to form nanoparticles of varying sizes) or a top-down approach (where synthesis starts with bulk material and is reduced to produce nanoparticles). These synthetic techniques include chemical, physical, and biological synthesis methods.

4.2.1. Physical Synthesis

Methods for synthesizing IONPs usually primarily follow the "top-down" approach, which includes techniques like laser evaporation, mechanical milling, and wire explosion. Laser evaporation, a simple method, produces nanoparticles by condensing material from either a gaseous or liquid phase.[256] This method is cost-effective and boasts higher yield while being environmentally favorable. Milling is an easy and user-friendly method that yields NPs via grinding. Among mechanical milling methods, ball milling stands out as convenient, affordable, very effective, and sustainable.[257] Its main drawback lies in the insufficient purity of the resulting product. Wire explosion, which entails the vaporization of a metal wire under high electric current, offers a compelling physiochemical method.[258] Yet, this approach also carries drawbacks such as undesired contaminants in the product, the need for intense energy, and the yields containing nonhomogenized IONPs.[259]

4.2.2. Chemical Synthesis

The chemical synthesis methods for IONPs predominantly employ bottom-up approaches, which include co-precipitation, electrochemical deposition, thermal decomposition, sono-chemical decomposition, microwave irradiation, aerosol methods, sol-gel techniques, hydrothermal and solvothermal methods. These approaches are extensively utilized in IONPs synthesis due to their numerous benefits, such as reduced handling complexities, precise control over morphology, amounts, and the possibility of enhancing yields, cost-effectiveness, and consistency of production method. The coprecipitation technique for synthesizing IONPs entails the precipitation of metal oxides, yielding Fe_3O_4, to develop IONPs ranging from 30 to 100 nm. The co-precipitation involves utilizing a ratio of Fe (II) to Fe (III) at 1:2.[260] It involves the gradual or rapid addition of an alkaline solution, resulting in the precipitation of magnetite (characterized by its black color). Magnetite is prone to oxygen, leading to its conversion into maghemite. Therefore, conducting this procedure in the presence of nitrogen is crucial. Magnetite and maghemite exhibit differences in structure, resulting in distinct net spontaneous magnetization (92 emu g^{-1} for magnetite and 78 emu g^{-1} for maghemite) of the synthesized IONPs at 300 K.[261] The nucleation and growth during co-precipitation adhere to LaMer's model.[262]

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O \quad (1)$$

The Fe_3O_4 may be oxidized in the presence of oxygen.

$$Fe_3O_4 + 0:25O_2 + 4:5H_2O \rightarrow 3Fe(OH^-)^{3+} \quad (2)$$

Since this process does not demand high temperature or pressure and boasts a high yield, it presents a significant advantage regarding industrial scalability. However, challenges such as aggregate formation, high pH, and yield variability continue to hinder the process from being the ideal synthesis approach.

The thermal decomposition method involves synthesizing IONPs at elevated temperatures using organometallic sources. This process yields IONPs with excellent crystallinity, defined shape, and controlled morphology. The optimizations are done by altering various parameters such as the type of surfactant and solvent, reaction duration, aging period, and temperature to achieve the optimal morphology.[263] This method is regarded as one of the most efficient techniques, which enables the scalability of IONPs with uniform characteristics. Another investigation delved into the thermal decomposition process of hydrated and dehydrated $FeSt_2$ and $FeSt_3$, analyzing how the ratio of sodium oleate (NaOl) to oleic acid (OA) introduced into the reaction medium influenced the outcomes.[264] The findings affirmed several key points: first, that NaOl effectively catalyzed the formation of nanoparticle shapes; second, that the composition of the precursor played a role, with $FeSt_2$ promoting the production of nanoplates and $FeSt_3$ favoring nanocubes; and third, that hydration hindered the formation of anisotropic shapes, necessitating a higher concentration of NaOl to achieve such shapes from highly hydrated precursors, likely due to ligand-water interactions forming micelles. Consequently, dehydrated precursors offered superior control over the resultant shapes.

The sol–gel is also heat dependent synthesis technique. In this approach, metallic salts are dispersed in desired solvents under undisturbed agitation to achieve a well-distributed sol. Subsequent steady warming enhances particle chemistry, including van der Waals forces, resulting in the formation of a gel.[265,266] Unlike other methods, the sol–gel process does not require sophisticated instruments and controlled heating, rendering it a cost-effective method. Moreover, it offers great control over the composition and morphology of IONPs. IONPs synthesized via this method typically exhibit good purity, crystallinity, and adjustability. However, there's a possibility of generating byproducts under specific conditions, necessitating additional purification steps to obtain pure IONPs. Furthermore, the sol-gel is considered a time-consuming method and also involves toxic solvents.

Hydrothermal synthesis is an efficient solution-based process for IONPs production under controlled heat and pressure.[267] The technique facilitates the generation of uniformly sized IONPs by regulating the solubility of minerals in solution, thereby regulating of crystal formation.[268] This method is favored compared to sol-gel techniques due to its capacity to yield NPs with appropriate characteristics. However, the drawback is that this method requires a sophisticated instrument and environment with controlled pressure and temperature. IONPs synthesized via this method exhibit remarkable effectiveness in reinforcing or attenuating the superparamagnetic characteristics.[269]

The microemulsion method entails forming micelles, and the process may involve oil-in-water or reverse type, with the presence of surfactant between these two phases.[270] In water-in-oil microemulsions, the water is incrementally added and distributed within an oil by surfactant. Various elements, including temperature and ionic concentration, influence the overall morphology and crystallinity of produced IONPs.[271] In this study, to produce IONPs, the temperature was controlled up to 72 °C, and ≤0.184 M and ≤0.09 M concentrations of Fe^{3+} and Fe^{2+} were used, respectively. Cetyl Trimethyl Ammonium Bromide (CTAB) was used as the surfactant, and its higher concentration tends to change its shape from cubic to pentagonal to spherical. Although the precise cause of this change

was not explicitly stated, it provides valuable insights into factors to consider when aiming for an optimized shape. Vidal et al. emphasized the significance of utilizing surfactants such as oleylamine. They showcased a narrow size distribution of 3.5 ± 0.6 nm in monodisperse maghemite IONPs.[272] Additionally, IONPs synthesized through the microemulsion method display enhanced saturation in magnetization and smaller particle size.[273] Nevertheless, this approach presents limitations such as limited scalability and the lack of a consistent surfactant concentration, which could raise concerns regarding potential toxicity

The synthesis of IONPs through the sonochemical process is alleviated by the acoustic cavitation model, wherein bubbles form within a liquid medium. The appearance and collapse of these bubbles lead to IONP production. These ripples assist in exhibiting transient conditions, including heat, pressure, and cooling rates of approximately 10^{10} K/s.[274] The emergence of bubbles in the process is dictated by the vapor pressure of the solvent medium. Various ligands are used to produce IONPs ranging from 5 to 16 nm.[275] Vijaykumar et al. investigated the production of NPs from Iron (II) acetate, aiming to elucidate the mechanism behind IONPs formation. The IONPs demonstrated a magnetization of under 1.25 emu g^{-1}, showcasing superparamagnetic characteristics. The suggested mechanism implicated the production of H and OH radicals from ultrasonic waves and water vaporization. Additionally, H_2 and H_2O_2 were generated during the process, with H_2O_2 assisting in the oxidation of ferrous to ferric ions and forming Fe_3O_4 via OH radicals. The role of surfactants in IONPs formation has also been extensively studied. SDS, as employed in the production of IONPs, yields particles with an approximate size of 8.5 nm.[276] Agents such as PEG-6000 and oleic acid were also used to assist the IONPs production and capping.[277,278] Furthermore, desired modifications can also be made using this method. However, a significant drawback of this procedure is the non-homogeneous property and the necessity for heat treatment to increase the crystallinity of the particles.

4.2.3. Biological Synthesis

The biological synthesis of IONPs has attracted significant attention due to their environmentally friendly, efficient, and sustainable nature. IONPs produced through this process are relatively compatible with the host but often exhibit suboptimal solubility.[279] Here the synthesis of IONPs encompasses utilization of Prokaryotic cells, herb constituents, and animal sources.[280] Prokaryotic cell-based synthesis predominantly involves the surface assimilation of metal ions followed by reduction mineralization.[281] The herb-based synthesis relies on soluble constituents like alkaloids and phenolic compounds.[282,283] Magnetite, present in living systems, has a significant role in sensing the Earth's magnetic field for directional orientation.[284] Biologically synthesized IONPs find applications as catalysts in various processes such as photocatalysis and Suzuki-Miyaura reactions. Nonetheless, this method presents certain limitations and challenges related to solubility and relatively low yields of IONPs, which require further refinement.

4.3. Imaging Applications in Cancer

Comprehensive analysis of IONPs' contributions to MRI in cancer diagnostics. Medical imaging is crucial in both the diagnosis and evaluation of cancer treatments. IONPs have garnered significant attention in medical imaging owing to their exceptional biocompatibility, pharmacokinetics, and efficacy in facilitating both diagnosis and therapy. These IONPs, typically composed of either Fe_3O_4 or γ-Fe_2O_3 crystals with particle diameters ranging from 1 to 1000 nm, have undergone extensive investigation. By incorporating a hydrophilic shell, modified IONPs exhibit enhanced stability in the bloodstream, making them well-suited for biomedical imaging applications.[108,285] Over recent decades, various commercial products such as Ferumoxide, Ferucarbotran, Ferumoxytol, and Ferumoxtran have become available.[286,287] This availability has facilitated the direct use of IONPs in clinical settings or "off-label" applications in medical imaging, rendering them more advantageous than alternative candidates. The molecular imaging approach involves analyzing and quantifying biological processes at the molecular or cellular scale, utilizing various imaging technologies such as optical imaging, ultrasound (US), MRI, CT, PET, SPECT, and PA imaging.[288,289] Since no single imaging method can offer comprehensive insights into both the structure and function of a subject simultaneously, researchers have developed multiple imaging modalities that combine different techniques. The rapid advancement of nano theranostics, which integrates imaging and therapeutic systems, has been considered an effective strategy for achieving personalized medicine.[290,291] IONPs serve as versatile multifunctional probes for various imaging applications and adaptable platforms for chemotherapy, phototherapy, and gene therapy by incorporating desired molecules, nanomaterials, or genes.

4.3.1. MR Imaging

Currently, a substantial and swiftly progressing field revolves around employing IONPs as contrast agents in MRI applications.[292] MRI, well-known for its exceptional spatial resolution and tomographic capabilities, remains a powerful non-invasive imaging technique. However, to enhance the sensitivity of MRI for the proper visualization of targeted tissue, contrast agents are crucial to accentuate the contrast between normal and diseased tissues. The primary benefit of MR contrast agents lies in their ability to decrease the T1 and T2 relaxation times, two distinct phenomena governing proton relaxation. T1 relaxation refers to longitudinal relaxation, while T2 relaxation pertains to the transverse relaxation of excited protons. The efficacy of a contrast agent in imaging is manifested through the reduction of T1 or T2 relaxation times, typically denoted by r1 or r2 relaxivity. Here, MR contrast agents can be categorized into two principal types: (i) positive contrast agents primarily aimed at diminishing the longitudinal T1 relaxation time while moderately affecting T2, thus producing bright MR images, and (ii) negative contrast agents principally focused on reducing the transverse T2 relaxation time, resulting in signal attenuation and darker MR images.

4.3.2. Dual-Modal Imaging

In certain scenarios, relying solely on a single imaging mode may not be sufficient to offer a comprehensive understanding for precise diagnosis. Multimodal imaging, which involves Incorporating multiple imaging approaches simultaneously into a unified approach, is increasingly favored for improving the early detection of cancer.[293] This combined technology facilitates the acquisition of anatomical details, including molecular insights, thereby enabling a thorough assessment of tumor characteristics, encompassing aspects such as localization, progression, morphology, viability, and more.[294] The available scanners to date are capable of performing integrated PET/CT, PET/MRI, and SPECT/MRI, which have unlocked the sensitive and precision capability of multimodal imaging techniques. For example, In the context of PET/MRI, a commercially available combined imaging technique, altered particles could prolong the lifespan and enhance the targeting efficiency of radiotracers, thereby extending the overall visualization time. Furthermore, utilizing IONPs enables functionalities such as drug delivery, hyperthermia, or photodynamic therapy, thereby imbuing PET/MRI with both therapy and diagnostic capabilities.

Given that CT provides superior spatial and high definition imaging compared to other technologies,[295] which urges the integration of MR and CT for precise imaging across various biological systems. Other metal nanoparticles, such as AuNPs, have garnered considerable attention due to their biocompatibility and high electron density, making them promising candidates for CT imaging applications.[296] The density of gold surpasses that of iodine, a constituent of widely used CT contrast agents like Omnipaque. Consequently, nanogold has emerged as a perfect CT contrast agent. In addition, various approaches have been employed to synthesize Fe_3O_4/Au NPs tailored for multimode MR/CT imaging applications. These include the development of Fe_3O_4–Au core-shell NPs, where gold is coated onto the surfaces of Fe_3O_4 NPs.

US imaging offers advantages such as real-time visualization, affordability, safety, and ease of integration. However, it has limitations, including poor penetration through bone, low resolution, and difficulty imaging gas-filled structures. Combining MRI with the US in a dual-mode imaging approach holds promise for providing richer pathological information and enhancing the accuracy of disease diagnosis. To address the limitations of US imaging, nano/microscale bubbles are commonly employed as contrast agents to improve backscattered acoustic signals and enable resonant scattering.[297] Recently, Fe_3O_4 nanoparticles have been incorporated into nano/microcapsules (NCs/MCs) to serve as multimodel contrast agents for imaging. For instance, a previous study prepared Fe_3O_4-containing MCs with diameters ranging from 2.30 to 9.24 µm by polymerizing butyl cyanoacrylate monomers and encapsulating Fe_3O_4 NPs within the poly(butyl cyanoacrylate) bubble shell using an oil in water encapsulation method.[298] Another study has developed Fe_3O_4-embedded NCs ranging in size from 180 to 230 nm using a one-step oil-in-water emulsifying process, with Pluronic F127 and PAA acting as the bubble shell.[299] These synthesized nano/microbubbles hold promise for in vivo MR/US imaging applications due to Fe_3O_4 and gas-filled bubbles within them.

4.3.3. Magnetic Particle Imaging

A cutting-edge imaging technique known as Magnetic Particle Imaging (MPI) generates three-dimensional (3D) images by detecting SPIONs administered into the body.[300] Unlike conventional imaging methods like MRI, X-ray, and CT, MPI doesn't primarily focus on structural imaging; rather, it functions as a tracer imaging system similar to PET and SPECT.[301] The versatility of SPIONs, owing to their ability to be conjugated with various molecules, opens up a wide array of potential applications. Additionally, residual magnetization without an external magnetic field enables precise remote control over their behavior, indicating their promise in oncological diagnosis and therapy.[28,302] In addition to that, MPI can visualize SPION accumulation in cancerous tissue solely through the EPR effect without the need for targeting strategies. It is widely acknowledged that the EPR effect varies significantly among individuals with the same tumor type and even over time during tumor progression.[235,303] Consequently, evaluating the fluctuation in the EPR effect by visualizing and quantifying the accumulation of nanomedicine in tumor tissue before treatment carries substantial importance. Likewise, concerning particle size, IONPs display comparable pharmacokinetic behavior and can co-localize with nano-formulations in perivascular regions. Recent findings have shown that ferumoxytol could precisely anticipate co-localization areas for PLGA-PEG nanoparticles within the TME, with an accuracy surpassing 85%.[304] Therefore, utilizing IONPs-enhanced quantitative MRI enables the monitoring of nanomedicine's tumor-targeting capability, aiding in the identification of sub-populations more inclined to respond to drug therapy in a simple and cost-effective manner.

Nevertheless, the typical issues associated with IONPs-based imaging impede their transition to clinical application. More efforts should be directed towards enhancing IONPs, focusing on improvements in pharmacokinetics and targeting capabilities, and refining imaging instruments to achieve better resolution, miniaturization, reduced cost, and increased intelligence. These advancements are essential for expediting the advancement of multimodal imaging techniques.

4.4. Targeted Drug Delivery and Hyperthermia in Cancer

Hyperthermia, a thermal cancer treatment, capitalizes on cancer tissues' heightened sensitivity to heat ranging from 42 to 45 °C compared to normal tissues. IONPs, due to their biocompatibility, respond to an AMF and serve as effective heat-generating agents.[305] Researchers have integrated these NPs with hydrogels, fiber sheets, and microparticles (MPs) to enhance their concentration at the target site for hyperthermia treatments.[306,307] Despite their potential for cancer hyperthermia therapy, these composite materials often lack strong adhesion to soft tissues under wet conditions, impeding stable retention of heat-generating agents at the cancer site. Additionally, the sprayability of materials is crucial for applications within the spatially confined gastrointestinal tract.[308] Thus, there is a demand for biomaterials capable of effectively targeting residual cancerous tissues at post-endoscopic surgery and exhibiting sprayable properties while adhering to soft tissues under wet conditions.

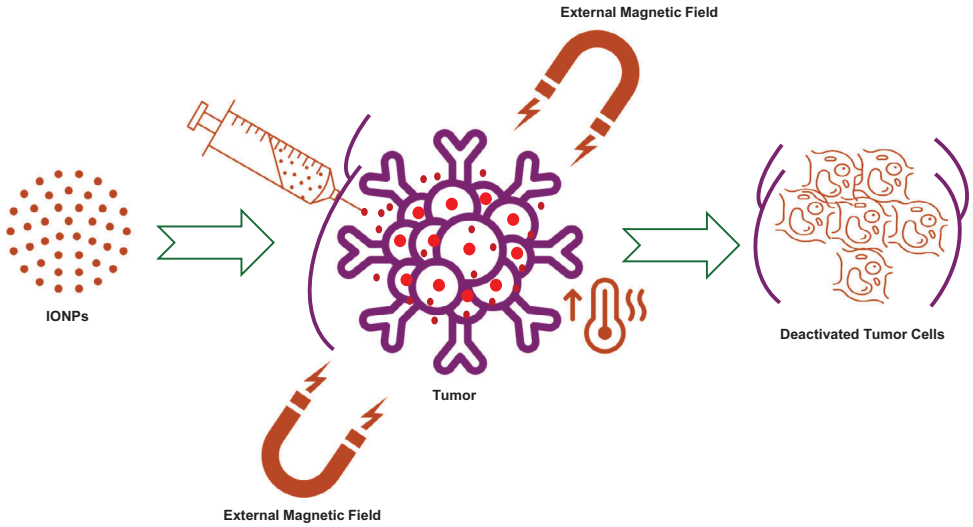

Figure 9. Schematic diagram illustrating hyperthermia and its role in neutralizing tumor cells. When IONPs are injected into the tumor and an external magnetic field is applied, the localized temperature increases, leading to the destruction of tumor cells.

Today, hyperthermia is utilized for the treatment of a range of cancers, including melanoma to urogenital cancers.[309] IONPs possess the ability to induce targeted hyperthermia. **Figure 9** demonstrates the potential of IONPs in hyperthermia for deactivation of cancer cells. They operate by raising the temperature within the targeted tumor, inducing thermal impairment to DNA and changes in cell membrane potential caused by disparities in sodium and potassium levels.[310] The heat is produced through Néel fluctuation, Brownian relaxation, hysteresis loss, and induced eddy currents due to rapid magnetic moments within the crystal lattice, depending on the applied AMF and the size of the nanoparticles.[311] Among various magnetic nanoparticles, superparamagnetic IONPs are mostly used for magnetic hyperthermia.[312] These nanoparticles can induce drug release in response to generated heat (e.g., Thermodox), or hyperthermia itself could trigger the release of drug or bioactive agents (e.g., Nanotherm). Presently, magnetic field-based hyperthermia is regarded as a promising method for drug delivery, demonstrated by the incorporation of DOX and IONPs into mesoporous silica, subsequently sealing the silica pores with a heat-sensitive molecule.[313] In situations where no drug release occurs at ambient temperature, magnetic hyperthermia triggers the uncapping of silica pores, facilitating drug release. This strategy is suggested to assist in the targeted treatment of cancerous tissue. Apoptotic signals may be observed in malignant and benign cells at temperatures ranging from 41 to 47 °C, while temperatures above 50 °C predominantly result in tissue alteration through necrosis rather than apoptosis.[314] The US FDA discontinued Feridex, an intravenous injection of iron oxide available commercially, citing economic and safety issues. Feridex functioned as both a hyperthermia agent and a contrast agent for MRI. Nonetheless, the heat generated in inductively coupled magnetic fields yields lesser thermal enhancement and necessitates a high iron oxide content. As a result, hyperthermia is linked with disadvantages such as the potential risk of harming benign tissue in close vicinity to the tumor due to the lack of optimization methods for the magneto-structural properties and magnetic dipolar interaction effects of IONPs, along with unreliable techniques for measuring hyperthermia.

Magnetic fluid hyperthermia (MFH) represents a modern approach to contemporary cancer treatment.[315] This treatment modality involves tumor-targeted hyperthermia by exposing it to IONPs and subjecting it to AMF.[305] IONPs in the nanoscale range (10–100 nm) are commonly utilized for MFH, as they possess the ability to generate localized heat when stimulated by an AMF. Remarkably, among nanomaterials, only IONPs have gained approval for medical use by both the US Food and Drug Administration and the European Medicines Agency due to their biocompatibility. The processes driving heat generation by magnetic nanoparticles in AMF predominantly involve two phenomena: hysteresis losses and relaxation processes.[316,317] Néel relaxation contributes to heat generation due to rapid shifts in the orientation of magnetic moments in relation to the crystal lattice, whereas Brownian relaxation arises from the physical rotation of nanoparticles within the surrounding medium.[318] To ensure efficient hyperthermia treatment, it's crucial to employ nanoparticles with high heating efficiency, which is greatly influenced by nanoparticle size, concentration, and the viscosity of the medium.[317,318] In clinical oncology, achieving a high specific absorption rate is crucial, but it is equally important to ensure safety by using the least nanoparticle concentration and biocompatible AMF to minimize the undesired effects.[319] The rates at which energy dissipates from nanoparticles to the treated tissues are crucial for the success of clinical treatment.

Traditional chemotherapy often encounters limitations such as poor targeting and drug resistance.[320] In this context, SPIONs are demonstrated to have potential in targeted drug delivery in response to magnetic fields. Recently, the photothermal conversion property of SPIONs, which allows them to convert light into heat, has been employed for generating mild hyperthermia, releasing bioactive substances, and providing iron.[321] SPIONs can act as an external source of iron to trigger ferroptosis, a mechanism in which lipid peroxidation impacts drug efflux, thereby combating tumor drug resistance.[322] Therefore, SPIONs show

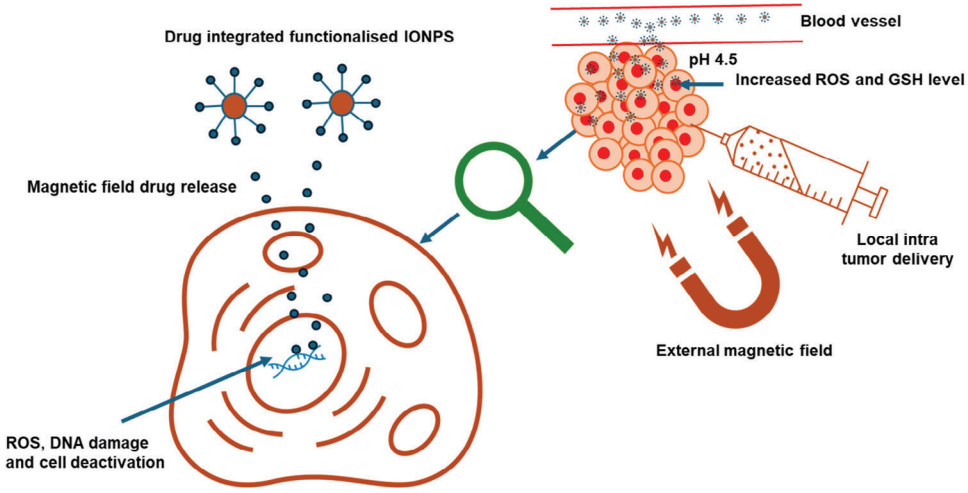

Figure 10. Diagram demonstrating the use of IONPs for targeted drug release to tumor cells. When drug-loaded IONPs are injected, the drug is released either in response to the acidic pH at the tumor site or through the application of an external magnetic field, enabling controlled and targeted drug delivery.

promise as ferroptosis-inducing nano agents by synergizing tumor therapies. Surface functionalization of SPIONs enables the attachment of linkers, receptors, drug molecules, and more, facilitating the coating of these nanoparticles with specific drugs for targeted delivery.[323,324] This approach also involves tagging the nanoparticles with receptors recognized by malignant and tumor cells, facilitating their absorption by these cells and providing a convenient approach for employing SPIONs as carriers for drug delivery.[325]

Targeted drug delivery systems have employed various carriers for anticancer drugs, such as IONPs and naturally occurring biodegradable or non-biodegradable polymers.[326] These bioactive molecules either be sorbed onto the cargo systems or encapsulated within them, enabling delivery to a specific region through external magnetic stimulation. **Figure 10** depicts the IONPs-based drug delivery systems and their synergistic anticancer effect. An example of external stimuli is magnetic-induced drug release, which entails applying alternating high or low-frequency magnetic fields.[327,328] These fields can deeply penetrate biological tissues with minimal physical interaction. Consequently, they enable the visualization of magnetic materials via MRI using a static magnetic field and controlled drug release when combined with AMF. Typically, AMF-triggered drug delivery relies on magnetic materials' ability to convert electromagnetic energy into thermal energy. Numerous studies in literature utilize systems comprising magnetic materials encapsulated within polymers capable of altering their structure in response to temperature changes. These systems find applications in treating diseases such as cancer and preventing post-surgical infections.[329]

DOX, an extensively studied anticancer medication, can be administered through IONPs coating, incorporating various linker agents such as folic acid and chitosan.[330] This approach aims to optimize IONPs stabilization, solubility, and efficient and targeted drug delivery, generally evaluated through cytotoxicity assays. A recent study developed a therapeutic nano platform through a simple production method.[331] This technology relies on magnetic micellar nanoparticles capable of dissociating and releasing drugs in the presence of a reducing agent, exerting potent anti-tumor effects. The technology combines SPIONs with multiple functionalities. Primarily, it can convert light from near-infrared wavelengths into heat, which locally warms the tumor site. This promotes drug release and boosts the effectiveness of chemotherapy against tumor cells. Secondly, it triggers ferroptosis in tumor cells. Thirdly, it prompts macrophages to adopt the pro-inflammatory M1 phenotype, intensifying ferroptosis in tumor cells. Lastly, it aids in loading DOX for combination therapy comprising chemotherapy and other treatments. The synergistic combination of these functions resulted in notable ferroptosis and growth inhibition in mouse bladder cancer cells. Furthermore, DOX has been utilized with lipid materials and IONPs to create magnetic field-sensitive lipocomplexes for targeted drug delivery aiming for the treatment of colorectal carcinoma in mice.[332,333] Findings have demonstrated enhanced anticancer efficacy with the magnetic lipocomplexes, coupled with increased cellular uptake, compared to conventional DOX administration. An essential aspect of an efficient cancer treatment regimen involves achieving desired treatment outcomes without harming the benign cells. This goal can be realized through targeted drug delivery to malignant tissue. A promising approach to functionalization entails using thermosensitive molecules as connectors for drug loading, enabling drug release when the temperature exceeds a critical threshold.[334] The following study demonstrates the effective synthesis and evaluation of a photothermal Fe_3O_4@PDA@BSA nanocomposite responsive to NIR laser intended for controlled drug release. This composite offers theranostic capabilities and holds promise for melanoma cancer therapy.[335] The main aim was to evaluate its efficiency as both a T2 MRI contrast agent and a therapeutic instrument through in vitro and in vivo assessments. The objective of this study was to investigate the synergistic effect of hyperthermia and low concentrations of DOX on melanoma cells. Combining photothermal and chemotherapy treatments using Fe_3O_4@PDA@BSA-DOX, together with laser irradiation, or utilizing a single chemotherapeutic approach with free-DOX or Fe_3O_4@PDA@BSA-DOX, notably slowed down tumor growth progression. This outcome

stemmed from the sensitivity of the drug-carrying cargo to the acidic ambiance within the tumor. However, the findings indicated that the efficacy of Fe_3O_4@PDA@BSA-DOX/Laser in combating cancerous tissue surpassed that of previous therapies, including free DOX, leading to a remarkable reduction in tumor size compared to tumor size before exposure to the drug.

Chlorambucil, identified as another promising agent for IONPs led delivery, as therapeutic approach for the treatment of chronic lymphocytic leukemia, Hodgkin's lymphoma, and non-Hodgkin's lymphoma.[336,337] Chlorambucil was also integrated into IONPs coated with a chitosan shell, exhibiting enhanced drug release onto cancerous cells in comparison to the free form of the drug.[337] Similarly, in another study, the antitumor drug violamycin was incorporated in IONPs measuring 8–10 nm in size, demonstrating enhanced effectiveness against the MCF-7 breast cancer cell line.[337] Similarly, in another study, the antitumor drug violamycin was incorporated in IONPs measuring 8–10 nm in size, demonstrating enhanced effectiveness against the MCF-7 breast cancer cell line.[338] These findings underscore the potential of utilizing such NPs led technology for drug delivery. Ferumoxytol is recognized as a highly efficient magnetic drug carrier with applications in image-assisted delivery of bioactive molecules, diagnosis, and treatment, demonstrating significant therapeutic outcomes, especially in cancer management. In a recent study, DOX, ferumoxytol, and medical chitosan (MC) were combined to create a magnetic hydrogel (DOX@FMT-MC) for tumor therapy through hyperthermia and synergistic chemotherapy.[339] DOX was conjugated to the hydroxyl group on the surface of ferumoxytol, resulting in a complex with MC to construct the hydrogel. In the acidic TME, DOX could be released gradually in response to pH alterations. Experimental findings, both in vitro and in vivo, indicated that DOX@FMT-MC showed a notable synergistic inhibitory effect on tumors. Moreover, as this hydrogel complex comprises clinically approved molecules and nanomaterials, it holds considerable promise for clinical use in the future. Furthermore, they developed thermosensitive magnetic liposomes by merging DOX-incorporated liposomes and ferumoxytol. The remarkable magnetic sensitivity of ferumoxytol renders it an excellent heating agent for creating these magnetic liposomes. The thermosensitive groups on the liposomes can respond to heat, liberating the loaded DOX and thus enabling the dual-mode synergistic effect of chemotherapy and magnetic hyperthermia in tumor treatment. Another research project highlights an innovative SPION-based "off-on" theranostic drug delivery system embellished with BPD as a photosensitizer, facilitated by an acid-labile hydrazone linker, and targeted with either Anti-EGFR ScFv or GE11 peptide.[340] Unlike "always on" agents, where BPD molecules are constantly active, the vicinity of BPD molecules on the surface of SPION results in fluorescence quenching, maintaining the system in the "off state" until taken up by the target cell through receptor-mediated endocytosis. Upon entry into the lysosome with its low pH, the acid-labile hydrazone bond undergoes cleavage, releasing BPD from the system. As BPD molecules disperse, fluorescence is restored, transitioning the system to the "on state." The amplified fluorescence signal serves as an indicator for system activation, signaling the initiation of treatment and imaging. Moreover, the presence of targeting moieties significantly enhances internalization, reducing nonspecific toxicity and fluorescence, thereby amplifying the efficacy of the theranostic agent. The presented activatable theranostic system provides multi-modal imaging capabilities and improved therapeutic efficacy for identifying and eliminating microtumors that express EGFR at high levels. It is widely recognized that the cytotoxic effects of IONPs involve inducing oxidative stress, as they prompt the generation of radicals such as HO• via Fenton Reaction, which arises from the interaction of iron ions with H_2O_2.[341] Research has explored combination therapy utilizing nanomaterials containing iron to accelerate oxidative stress, coupled with active agents to mitigate cells' response to stress, aiming to gain higher cytotoxicity against malignant cells. The amalgamation of IONPs with antitumor molecules has demonstrated the ability to generate oxidative stress leading to DNA damage and apoptosis in cancer cells.[299,342] Additionally, employing a nanocarrier containing a ROS scavenging inhibitor alongside a ROS generator has been shown to diminish cell viability and induce apoptosis in the MDA-MB-231 breast cancer cell line.[343] In this scenario, IONPs present a viable strategy for inducing oxidative stress in cancerous cells, owing to their possibilities of surface modification and functionalization to achieve more targeted interactions.

A recent study also highlights the cumulation of Dimercaptosuccinic acid-IONPs within the lysosomes of microglia cells, leading to the generation of ROS and subsequent cytotoxicity due to the rapid degradation of IONPs and the release of iron, driven by the lower pH at lysosomes.[344] Notably, this cytotoxic effect was reversed upon neutralizing the lysosomal pH or treating cells with an iron chelator. Additionally, it was found harmless to astrocytes or neurons, where these nanoparticles were not found to be assembled in lysosomes, underscoring the role of iron degradation in lysosomes in ROS production and IONP-induced cytotoxicity. Another study achieved successful integration of mGEF@Fe_3O_4 NPs by chemically conjugating the synthesized mGEF chemo drug to Fe_3O_4 NPs.[345] The direct chemical coupling of the drug with nanoparticles significantly improved loading efficiency, leading to enhanced drug internalization by PC9 lung cancer cells and subsequently improved chemotherapeutic effectiveness, with an estimated IC50 value of 2.0 μM for mGEF@Fe_3O_4 nanoparticles. Additionally, MRI and PET/CT imaging analyses were conducted, revealing a higher accumulation of NPs in the outer region of the tumor compared to the inner region, attributed to necrosis within the inner tumor region. Analysis of in vivo biodistribution showed the successful elimination of nanoparticles after treatment without any harmful effects on the body's major organs. Overall, integrating chemically linked drug delivery on nanoparticles with image-guided methods can mitigate concerns regarding drug leakage and improve insight into the therapeutic outlook for tumors, thereby advancing the efficacy of chemotherapy in future cancer treatment endeavors.

LSPR is a unique photophysical phenomenon observed in metallic nanostructures, commonly referred to as plasmonics. In LSPR, the oscillating magnetic field of electromagnetic radiation prompts the conduction-band electrons on the surface of a particle to oscillate collectively when interacting with a plasmonic material. This oscillation leads to heat generation, with the maximum amplitude occurring at a specific wavelength known as the LSPR peak. Various shapes such as nanorods, nanoshells, nanostars, nanocages, and cluster configurations have been

employed for applications including PTT, targeted drug delivery, controlled drug release, and other tumor treatment in vivo models.[346,347] A recent investigation explores the anticancer capabilities of IONPs coated with glucose and linked with Safranal (Fe_3O_4@Glu-Safranal NPs) on a liver cancer cell line.[348] The study characterizes the anticancer effects of Fe_3O_4@Glu-Safranal NPs on liver cancer cells. The findings here demonstrate that Fe_3O_4@Glu-Safranal exhibits notable antiproliferative properties against cancer cells, eliciting anticancer effects through mechanisms involving cell cycle arrest and induction of apoptosis. Considering the biocompatibility of the nanoparticles' constituent compounds, their magnetic characteristics, and their proven ability to inhibit cancer cells, Fe_3O_4@Glu-Safranal NPs show potential for further investigation in both in vitro and in vivo experiments targeting liver cancer. Similarly, another study introduced a pH-responsive and size-shrinkable drug delivery system for tumor chemotherapy.[152] This system, termed self-assembled iron oxide aggregates (SIOA), was constructed by incorporating hydrophobic *N,N*-dibutalamino ethylamine (DBE) and hydrophilic mPEG onto ultrasmall Fe_3O_4 nanoparticles. Under physiological pH conditions, the modified Fe_3O_4 nanoparticles underwent aggregation, resulting in a substantial increase in size to ≈220 nm. However, within the acidic microenvironment, SIOA disaggregated into ultrasmall Fe_3O_4 nanoparticles, facilitating the accelerated release of DOX and Fe^{2+}, consequently boosting the production of •OH. The size reduction of SIOA-DOX led to heightened cytotoxicity, prolonged retention, and enhanced penetration into tumor sites, displaying superior antitumor efficacy compared to SIOA, DOX, and Fe_3O_4 nanoparticles. The pH-responsive self-assembled aggregations offer a safe and highly efficient approach for achieving a balance between tumor accumulation and deep penetration, holding significant potential for cancer chemotherapy.

4.5. Challenges with IONPs in Cancer Applications

The U.S. Food and Drug Administration (FDA) has approved several IONPs for clinical applications. These include Feraheme for addressing iron deficiency, Combidex (in the U.S.) and Sinerem (in Europe) as MRI agents, Nanotherm (MagForce) for cancer therapy, and Lumirem as an imaging agent for the oral gastrointestinal tract. Among these, Feraheme (ferumoxytol injectable solution) was approved in the U.S. in 2009, in Canada in 2011, and in Europe in 2012.[349] It has been employed to address iron deficiency anemia (IDA), especially among patients with renal impairment. Moreover, ferumoxytol shows potential for various other biomedical uses, such as enhancing MRI imaging, delivering drugs, treating oral biofilms, and developing therapies for various cancers and inflammation. Notably, ongoing clinical trials are employing ferumoxytol as an MRI contrast agent.[350] These investigated nanoparticles displayed the least cytotoxicity under standard conditions without AMF, which conflicts with the results reported in previous studies.[351] Nevertheless, their cytotoxicity was observed to rise notably upon exposure to an AMF, indicating that iron nanoparticles, despite their FDA approval, pose challenges regarding their long-term in vivo biotransformation.[352] With repeated treatment, there is a potential for redistribution into the bloodstream and adjacent healthy tissues, resulting in local cumulation.[353] Therefore, it is advisable to administer IONPs directly into the tumor or functionalize them for targeted delivery to improve treatment effectiveness and reduce side effects. In therapies involving nanoparticles that are challenging to eliminate, achieving optimal therapeutic effects with minimal doses is vital. Furthermore, given that magnetic hyperthermia using nanoparticles is conducted in a clinical setting where patients are subjected to a magnetic field, it is crucial for nanoparticles used in magnetic fluid hyperthermia not to cause cytotoxic effects beyond the therapy duration in the clinic. The primary obstacles in IONPs hyperthermia pertain to delivery and energy deposition. Thermal nanomedicines are composite products comprising an injectable drug-like component that necessitates delivery to the tumor (either systemically or directly). Subsequently, this component is activated by an energy source to induce localized heating in the targeted treatment area. The generated heat may serve to trigger the release of the drug (as seen in ThermoDox), or it can function as the therapeutic agent itself (as demonstrated by NanoTherm).[354] The process of delivering nanoparticles to the tumor, whether via systemic circulation or local administration, entails various biological mechanisms influenced by the physicochemical properties of the nanoparticles, thereby impacting their performance. For magnetic hyperthermia, AMFs typically range from approximately 100 to 300 kHz. Frequencies lower than 10 MHz are minimally attenuated by tissues, yet the Joule heating resulting from induced eddy currents poses safety challenges regarding coil design and operation. Based on the tumor's placement in the patient and the nanoparticles' specific loss power, the interaction between the AMF and the tissue volume exposed could potentially result in substantial non-specific heating.[355] his indiscriminate heating might even match the heat produced by the nanoparticles, a situation considered clinically unacceptable. Consequently, there's an increased demand for nanoparticle development to enhance specific loss power and facilitate efficient delivery, all while adhering to clinical AMF design constraints.[356]

Although electromagnetic fields (EMFs) hold promises for therapeutic purposes, it is crucial to comprehend the potential risks associated with their exposure at high intensities and to utilize them only under appropriate conditions and with proper safeguards. AMFs can exert both in vitro and in vivo effects contingent upon various factors such as frequency, intensity, and duration of exposure.[357] These effects may encompass both advantageous and detrimental outcomes, with variations observed depending on the biological system under scrutiny. One of the most widely recognized biological consequences of AMFs involves the induction of eddy currents within tissues. At elevated frequencies and intensities, these currents can generate heat within tissues.

Before delving into combination therapies involving these nanoparticles, it is essential to consider the various synthesis techniques employed to fabricate them. The chosen synthesis method significantly influences the properties of nanoparticles, such as size, surface characteristics, and overall biocompatibility. These characteristics, in turn, dictate how effectively the nanoparticles interact with biological systems, how they can be functionalized with therapeutic agents, and how they behave in targeted drug delivery or other therapeutic contexts. Moreover, the synthesis method is not just a technical detail but a crucial determinant of nanoparticle performance in biomedical applica-

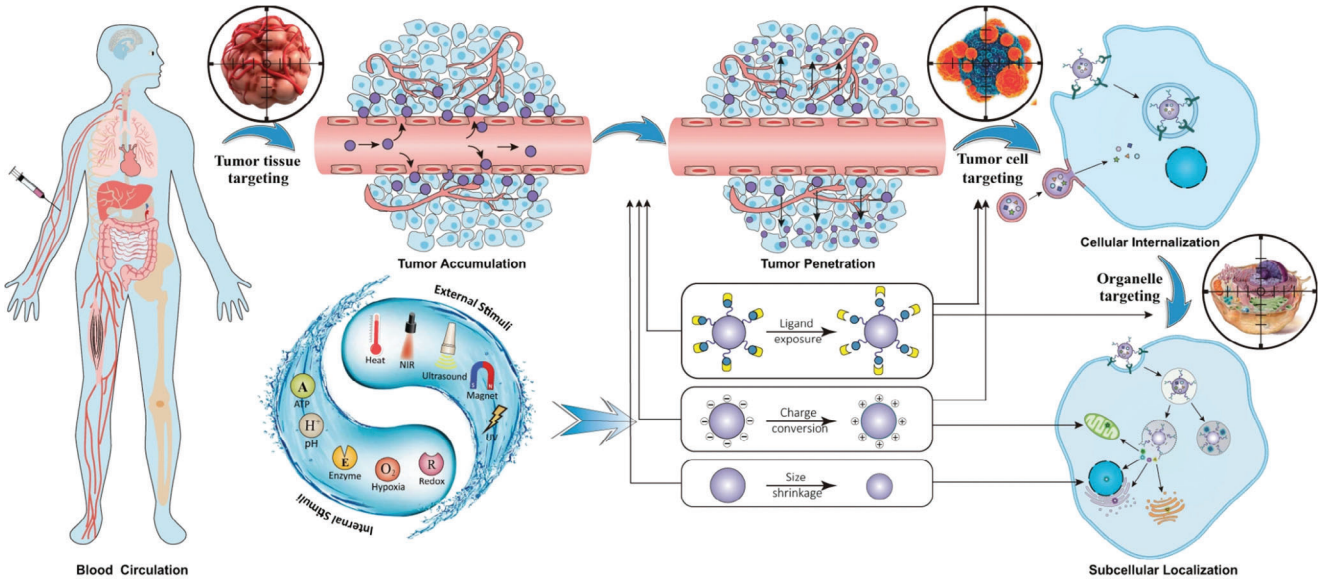

Figure 11. Maximizing therapeutic benefits of cancer nanomedicine through the stimuli-triggered dynamic integration of multistage tumor targeting was adapted from ref. [358] with permission. Copyright 2023, The authors, Nature, Creative Commons license.

tions. For instance, some synthesis techniques allow for greater control over particle size, while others focus on biocompatibility and sustainability, such as green synthesis methods that use plant extracts or bacteria. In the context of cancer therapy, where precision and biocompatibility are paramount, the choice of synthesis method can directly influence treatment efficacy and safety. By understanding the distinct advantages and limitations of each synthesis technique, researchers can better tailor nanoparticles to specific therapeutic needs. Thus, before exploring the role of these nanoparticles in combination therapies, it is valuable to compare the key synthesis methods used for AuNPs, AgNPs, and IONPs. **Table 1** provides a detailed comparison of these methods, highlighting their critical features, such as yield, scalability, purification needs, toxicity, functionalization potential, and environmental impact.

5. Combination Therapies Involving AuNPs, AgNPs, IONPs

5.1. Synergistic Approaches in Cancer Treatment

Combinational therapies are spotlighted for cancer treatment due to their anticancer effect at low concentrations and in drug-resistant cancer cells, whereas monotherapy often affects both healthy and cancerous cells. Although combinational therapy exhibits toxic effects, they can particularly be overcome by using natural anticancer drugs with biocompatible nanoparticles. In this line, several metallic nanoparticles have been recently spotlighted for their anti-cancer property due to their synergistic effects when combined with certain molecules such as natural products. However, when unique compounds/substances/therapies or nanoparticles are used individually, they don't exhibit significant anti-cancer properties due to decreased bioavailability and poor targeting. In addition, to enhance the delivery of drugs/biomolecules to target cells and to minimize off-targets, nanoparticles' physicochemical properties could be adjusted through the conjugation of biomolecules such as antibodies, peptides, and aptamers, respectively (**Figure 11**). Therefore, in this section, we have critically discussed various strategies to improve the synergistic effect of various bioactive compounds and mostly used metallic nanoparticles highlighted, which could provide deep insight into selecting treatment options for effective anti-cancer therapy.

5.1.1. AuNPs

As discussed above, AuNPs are recognized as key metal nanoparticles due to their customizable size, shape, surface charges, and strong affinity for thiol, amino, and carboxyl groups, enabling functionalization. Their ability to deliver multiple anticancer molecules makes them an effective delivery system. These properties make AuNPs widely used in treating malignant tumors through therapies like drug and nucleic acid delivery, PDT, PTT, and X-ray-based imaging. While using AuNPs alone, anti-cancer drugs/molecules possess low solubility, short life, development of drug resistance, and target selectivity, and their drawbacks can be overcome by applying combinational therapies. Therefore, various combinational therapies using AuNPs for efficient anticancer treatment can be considered and adapted previously. When DOX is conjugated with AuNPs, their drug-resistant characteristic can be masked.[359–363] Another study showed even the simplest conjugate of MTX with carboxylic groups of AuNPs could enhance anti-cancer properties, whereas free MTX reduced the anticancer effect at equal doses, indicating their synergistic effects.[364] Therapeutic antibodies, a cornerstone of targeted cancer therapy, also benefit from conjugation with AuNPs. Monoclonal antibodies (mAbs) conjugated with AuNPs offer advantages over mAb-based monotherapy by enhancing cytotoxicity toward cancer cells through increased oxidative

Table 1. Provides a comprehensive comparison of the synthesis methods used for AuNPs, AgNPs, and IONPs. The table highlights the advantages, disadvantages, purification needs, and environmental impact of each method, which ultimately influence their performance in clinical and preclinical applications. Understanding these differences is crucial as they shape the nanoparticles' behavior in biological environments, affecting their interaction with drugs, targeting ligands, and the TME.

Nanoparticle Type	Synthesis Method	Advantages	Disadvantages	Critical Features	Time	Scalability	Yield	Purification	Toxicity	Functionalization Potential	Environmental Impact	Applications
Gold Nanoparticles	Chemical Reduction	Simple, cost-effective, good size control	Toxic-reducing agents, environmental concerns	Highly reproducible, scalable	Minutes	High	High	Minimal	Moderate	High	High toxicity, generates waste	Drug delivery, cancer imaging
Gold Nanoparticles	Green Synthesis (Plant)	Eco-friendly, rapid synthesis, size and shape control biocompatible	Need raw/biological plant materials	Sustainable, good for biomedical applications	Few seconds to minutes	High	High	Minimal	Low	Moderate	Low toxicity, eco-friendly	Cancer therapy, biosensors, antimicrobial applications
Gold Nanoparticles	Green Synthesis (Bacteria)	Biocompatible, eco-friendly	Slow, longer process times, more complex	Potential for large-scale, biocompatibility	Hours to days	Moderate	Moderate	Extensive	Low	Moderate	Low toxicity, requires culture waste disposal	Drug delivery, targeted therapies
Gold Nanoparticles	Seed-Mediated Growth	Precise control over particle size and shape	Requires multiple steps	Allows synthesis of anisotropic shapes	Hours	Low	Moderate	Moderate	Low	High	Medium waste, energy-intensive process	Photothermal therapy (PTT), cancer imaging
Silver Nanoparticles	Chemical Reduction	Simple, scalable	Use of toxic chemicals	Size and shape control through reaction parameters	Minutes	High	High	Minimal	Moderate	High	High toxicity, hazardous waste	Antimicrobial coatings, cancer therapy
Silver Nanoparticles	Green Synthesis (Plant)	Environmentally friendly, biocompatible	Need raw/biological plant materials	Sustainable, rapid reaction	Few seconds to minutes	Moderate	Moderate	Extensive (biological residues)	Low	Moderate	Low toxicity, eco-friendly	Antibacterial agents, anticancer treatment
Silver Nanoparticles	Green Synthesis (Bacteria)	Biocompatible, eco-friendly	Slow process, limited size control	Biocompatibility, stable particle size	Hours to days	Low	Low	Extensive (biological residues)	Low	Moderate	Low toxicity, requires culture waste disposal	Cancer therapy, antibacterial agents

(*Continued*)

Table 1. (Continued)

Nanoparticle Type	Synthesis Method	Advantages	Disadvantages	Critical Features	Time	Scalability	Yield	Purification	Toxicity	Functionalization Potential	Environmental Impact	Applications
Iron Oxide Nanoparticles	Co-precipitation	Simple, low-cost, scalable	Poor control over particle size	Suitable for large-scale production	Minutes	High	High	Minimal	Moderate	High	Moderate environmental impact	MRI contrast agents, hyperthermia therapy
Iron Oxide Nanoparticles	Green Synthesis (Plant)	Eco-friendly, biocompatible, low-cost	Need raw/biological plant materials	Uses plant extracts for reducing agents	Few seconds to minutes	Moderate	Moderate	Extensive (biological residues)	Low	Moderate	Low toxicity, eco-friendly	Drug delivery, cancer treatment
Iron Oxide Nanoparticles	Green Synthesis (Bacteria)	Eco-friendly, biocompatible, slower process	Size/shape control challenges	Stable particles, but longer synthesis times	Hours to days	Low	Low	Extensive (biological residues)	Low	Moderate	Low toxicity, requires culture waste disposal	Cancer therapy, MRI contrast, drug delivery
Iron Oxide Nanoparticles	Thermal Decomposition	Produces highly crystalline particles	Requires high temperatures, complex solvents	Uniform shapes	Hours	Low	High	Moderate	Moderate	High	High energy consumption and waste	Cancer therapy, drug delivery, MRI contrast agents
Hybrid Nanoparticles	Green Synthesis	Eco-friendly, biocompatible, multifunctional	May involve complex biological materials	Sustainable, for drug delivery and imaging	Few seconds to minutes	Moderate	Low to moderate	Moderate	Low	Moderate	Low toxicity, eco-friendly	Theranostics, drug delivery, cancer imaging
Hybrid Nanoparticles	Template-Assisted Synthesis	Produces well-defined shapes	Requires additional steps for template removal	Hollow or porous nanoparticles	Hours	Low	Moderate	High	Low	Moderate	High waste generation due to template removal	Drug delivery, imaging contrast agents, early cancer detection

stress and autophagy, leading to higher therapeutic efficacy. Furthermore, combining therapeutic drugs with mAb-AuNP conjugates enables a dual antibody/drug action, resulting in synergistic effects that further enhance cancer treatment outcomes.[365,366]

Gene therapy delivers nucleic acid to cancer cells to prevent or treat them by employing foreign RNA and DNA. However, nucleic acid medications are vulnerable to increased environmental concerns, including enzymatic, chemical, and physical degradation during gene editing and transfection. Further, biologic drugs are prone to immunogenicity and target innate immune cells. Henceforth, to prevent immunological response and prevent nucleic acid degradation, non-viral vectors such as AuNPs are used to prevent DNA from fragmentation and physical damage with increased cellular uptake up to 99%.[365,367–369] Various studies have demonstrated photothermal and dual functional delivery platforms of AuNPs and gene and chemotherapy drugs to attain synergistic effects. Further, using PEG and hyaluronic acid (HA) minimizes toxicity to the major organs through targeted therapy with enhanced antitumor effects compared to single therapy.[370]

PDT has been considered relatively safe and effective in treating damaged and diseased cells. However, they possess certain drawbacks, including low water solubility, the ability to aggregate in physiological conditions, greatly affecting quantum yield $^1O_2$, and non-specific distribution in vivo. Hydrophilic PEG chains can be used to increase their aqueous solubility.[371,372] AuNPs can cause thermal damage to cancer cells by absorbing light at high (>43%) temperatures due to their SPR effect of free electrons.[373–375] When PTT is combined with chemotherapy, it exhibits significant cytotoxicity and tumor inhibition compared to the use of PPT or chemotherapy alone. Compared to visible light, using Near Infra-Red (NIR) is crucial as it possesses long wavelengths and, therefore, allows light to penetrate deep into living tissues with minimal damage to tissues.[367,376] In line with this, AS1411, an aptamer, was used to modify AuNPs and hairpin DNA loading with DOX designed to exhibit targeted and synergistic chemo-PTT to treat colon cancer. The results exhibited better anti-cancer effects compared to PTT or chemotherapy applications.

When PTT alone was used, it could not annihilate tumors as they generally use light wavelength less than (<700 nm), thus making it difficult to penetrate deep tumor tissues and thereby failing to obtain satisfactory results. Another reason is that $^1O_2$ generation requires sufficient oxygen supply within the tissue, often making photosensitizers (PSs) ineffective in the tumor site. Interestingly, PTT increases blood flow by increasing oxygen supply to tumor tissues. Hence, combining PTT with PDT can synergistically induce cytotoxicity in cancerous cells. However, this treatment limits its use in clinical practice as it requires two different types of wavelength lights, which complicates this strategy. To overcome this, it is necessary to identify the novel PTT and PDT agent that uses the same wavelength of light. The problem was recently solved by designing captopril-stabilized Au nanoclusters (Au_{25} $(Capt)_{18}$) as the PDT and PDT agent as they use a single wavelength (808 nm) as the single light source (**Figure 12**).

Another interesting study was published to explain the synergistic effect of PTT and radiotherapy (RT), which enhanced cancer cell lethality even at lower concentrations (**Figure 13**). This synergistic approach decreased X-ray-induced negative effects on the tumor and adjacent normal tissues.[378–380]

5.1.2. AgNPs

The application of AgNPs is well-established in medicine apart from their anti-microbial properties. AgNPs are spotlighted in treating cancers that become resistant to chemotherapy or radiotherapy when They are combined with various therapies or natural pharmaceuticals that contain anticancer properties due to their unique properties.[381] When AgNPs combined with ultrasound (US) waves exhibited synergistic effects against MCF-7 cells compared to individual treatment, US and AgNPs have the ability to promote ROS-induced cancer cell death.[382] Another study showed fungal mediated AgNPs with biochar exhibited increased synergistic cytotoxicity effect compared to AgNPs or biochar treatment in A549 cells.[383] Camptothecin (CPT) and its derivatives are the inhibitors of topoisomerase that are considered effective anticancer agents against various cancers when combined with DOX, ellipticine, and mAMSA, respectively.[384] In this regard, the combination of low concentrations of CPT and AgNPs enhanced cytotoxicity and apoptosis by increasing ROS generation, inhibiting cell proliferation, and altering mitochondrial membrane potential, improving survival rate compared to monotherapy.[385] Another combinational study demonstrated hydrogel nano-silver particle composite (AgNPs@C_MA_O) prepared using Ag, carboxymethyl chitosan (CMC), and poly(acrylic) acid co-maleic acid (MA) induced apoptosis mediated cell death when used at very low concentrations.[386] To achieve a specific carrier, carboplatin-added AgNPs showed an increased apoptotic effect compared to carboplatin or AgNPs-treated cells in vitro.[387] Also, the non-toxic concentration of AgNPs with gemcitabine (GEM) improved the therapeutic efficacy of GEM in triple-negative breast cancer cells.[388] The functionalization of NPs with biocompatible biomolecules has increased therapeutic efficacy. For instance, the functionalization of metal NPs with glutamine improved the biocompatibility of NPs and also increased the therapeutic efficacy of glutamine against colon cancer cells.[389] A one-pot synthesis of PF/HA-QtN#AgNPs improved water stability and stability of QtN and enhanced the targeting ability of AgNPs, indicating the better performance of PF/HA-QtN#AgNPs compared to free QtN and HA-QtN#AgNPs respectively. The synthesis of water-soluble HA-anchored folic acid/folate (FA) conjugated with PEG improved the intracellular concentration of AgNPs through the active transport of QtN to the perinuclear to nuclear regions of cells through endocytosis.[390] The targeted efficacy of epirubicin, a chemotherapeutic agent, was enhanced in conjugation with AgNPs and PVA polymer coating EPI/PVA/AgNPs. Later to radioiodinated ^{131}I isotope was conjugated to form ^{131}I–EPI/PVA/AgNPs improving the overall performance of tumor treatment. Thus, these findings offer ^{131}I–EPI/PVA/AgNPs, a promising system for treating solid tumors with enhanced target efficiency.[391] A chitosan/biogenic AgNPs conjugate exhibited improved anti-cancer properties compared to biogenic AgNPs against human cervical and adenocarcinoma cell lines, respectively.[392]

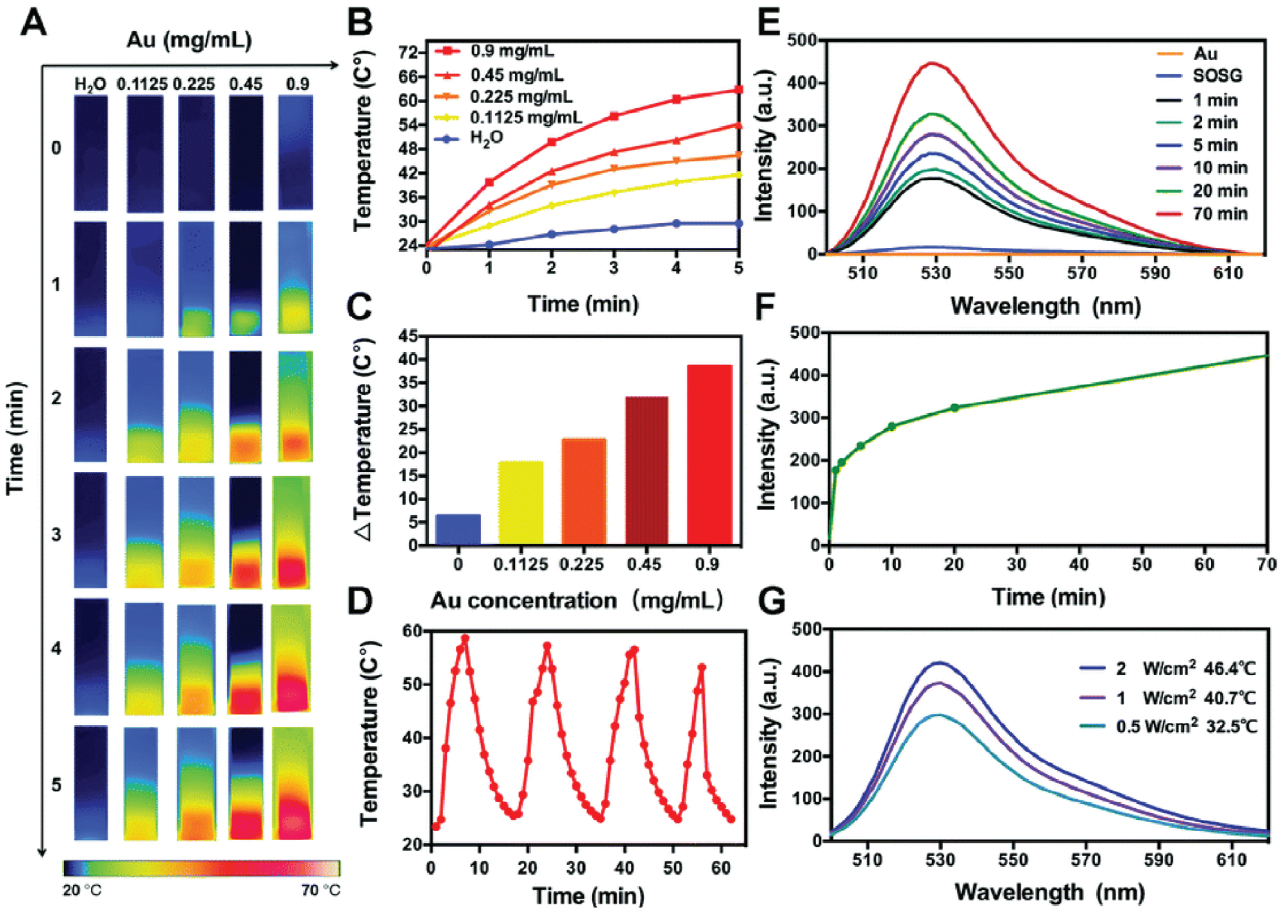

Figure 12. Photothermal and photodynamic effects of $Au_{25}(Capt)_{18}$ was adapted from ref. [377] with permission. Copyright 2019, Royal Society of Chemistry.

5.1.3. IONPs

IONPs are small with core sizes ranging from 10–100 nm and are referred to as "single super spin" with increased magnetic susceptibility. Three main functional components of IONPs are crucial to exhibit cancer treatment: 1) The core of IONPs must contain a medication or an MRI contrast agent. 2) The IONPs coatings must be biocompatible in nature. 3) The target ligand should be a biomolecule or pharmacological moiety capable of addressing over-expressed receptors on the cancer surface.[393] These functional properties have potential in cancer treatment. In this regard, several combinational approaches, such as CT, RT, and PT based on IONPs, can be selected in combination with gene therapy to treat cancers in a synergistic manner. For instance, the siPLK1-conjugated streptavidin-conjugated dextran-coated SPION (siPLK1-StAv-SPION) delivery platform has the ability to inhibit pancreatic cancer through initiating apoptosis by knocking down the expression of cell cycle-specific serine-threonine-kinase.[394] Further, the combined delivery of gene therapy along with CT drugs was used by several scientists to improve the killing effects on cancer cells via various molecular mechanisms, prevent cell death, and reduce toxicity to normal cells. For instance, co-delivery of ASO-miR-21 and GEM using PEG-PEI-coated IONPs to pancreatic cells significantly inhibited growth and metastasis of tumor cells through the upregulation of tumor suppressor genes PDCD4 and PTEN and inhibition of epithelial-mesenchymal transition. Further, immune cells can be combined with chemotherapeutic drugs to trigger immune responses after exposing exogeneous gene-drug-carrying IONPs to kill cancer cells.[395] In a recent study, Meng et al. used IONPs-C/O@LPs to activate immature dendritic cells to maturate (**Figure 14**).

Like AuNPs, IONPs are potential PT materials that can convert light energy into heat to eradicate tumor cells.[397,398] IONPs can also combine gene therapy and PT to accomplish tumor-killing effects in tumor cells for actin cytoskeleton fragmentation and apoptosis induction in non-small-cell lung cancer cells.[399] Additionally, IONPs have also been extensively studied to prove that they are radiosensitizers that minimize radiation to normal tissues by enhancing the target of cancer cells. For example, an IONP-based nanocarrier was designed to deliver anti-Ape1 siRNA to brain cells, which worked synergistically along with radiotherapy to improve the antitumor effect by downregulating multifunctional DNA repair enzyme apurinuclease 1 (Ape 1).[396]

5.2. Recent Advancements in Combined Nanoparticle Therapies for Cancer

When two or more metallic nanoparticles with different properties are combined into the same NPs, structural changes can

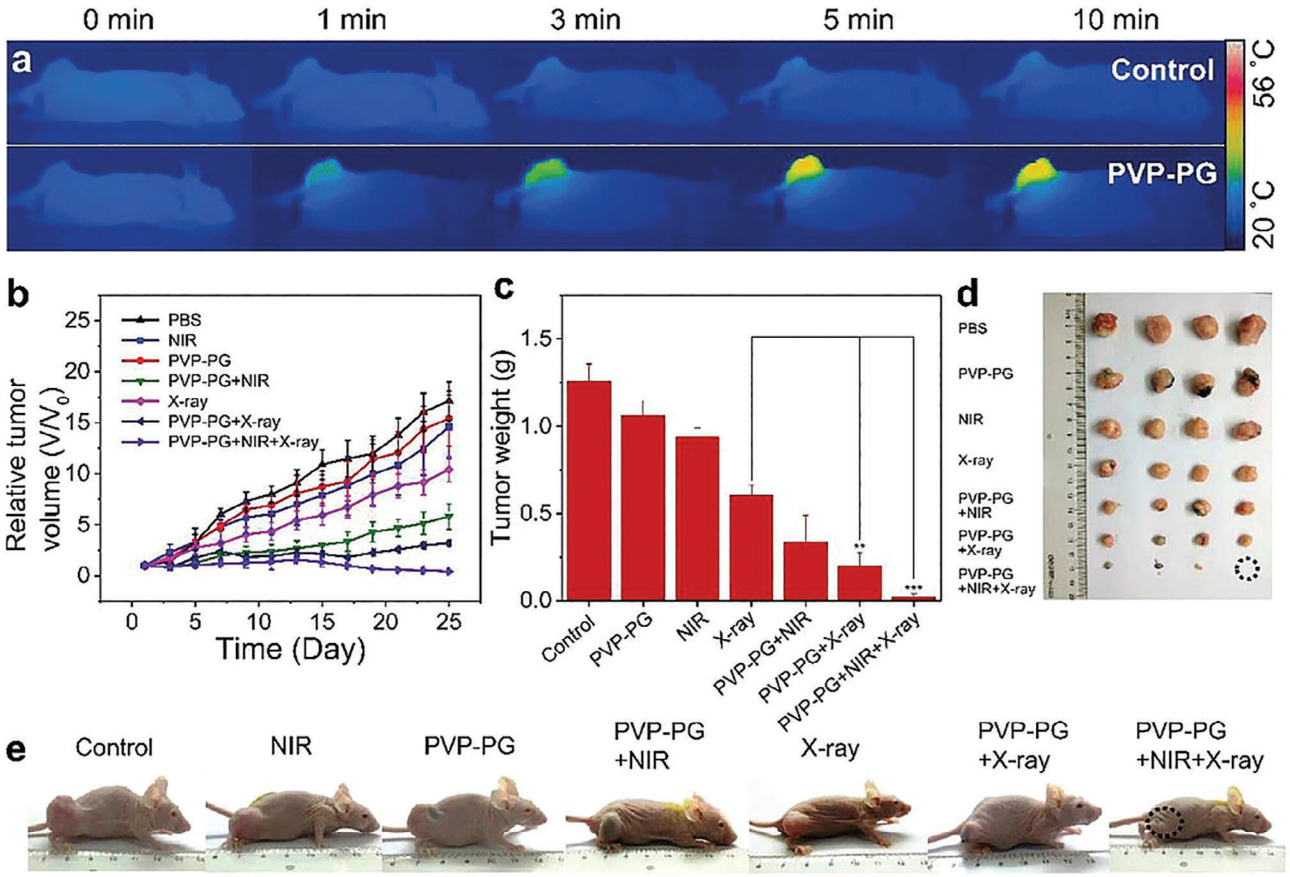

Figure 13. Combined RT and PTT in vivo studies were adapted from ref. [377] with permission.

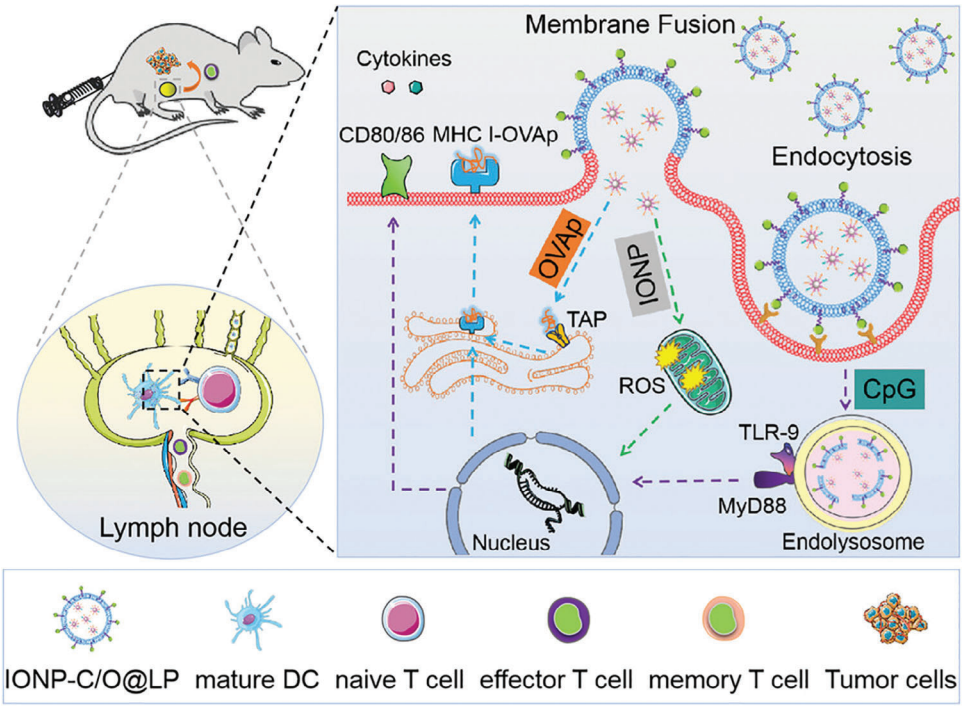

Figure 14. The synergistic effect and immune response elicited by IONP–C/O@LPs. IONPs co–delivered CpG DNA to active immature DCs, synergistically enhancing immune response and antitumor effect. This figure was adapted from ref. [396] with permission. Copyright 2022, Wiley-VCH GmbH.

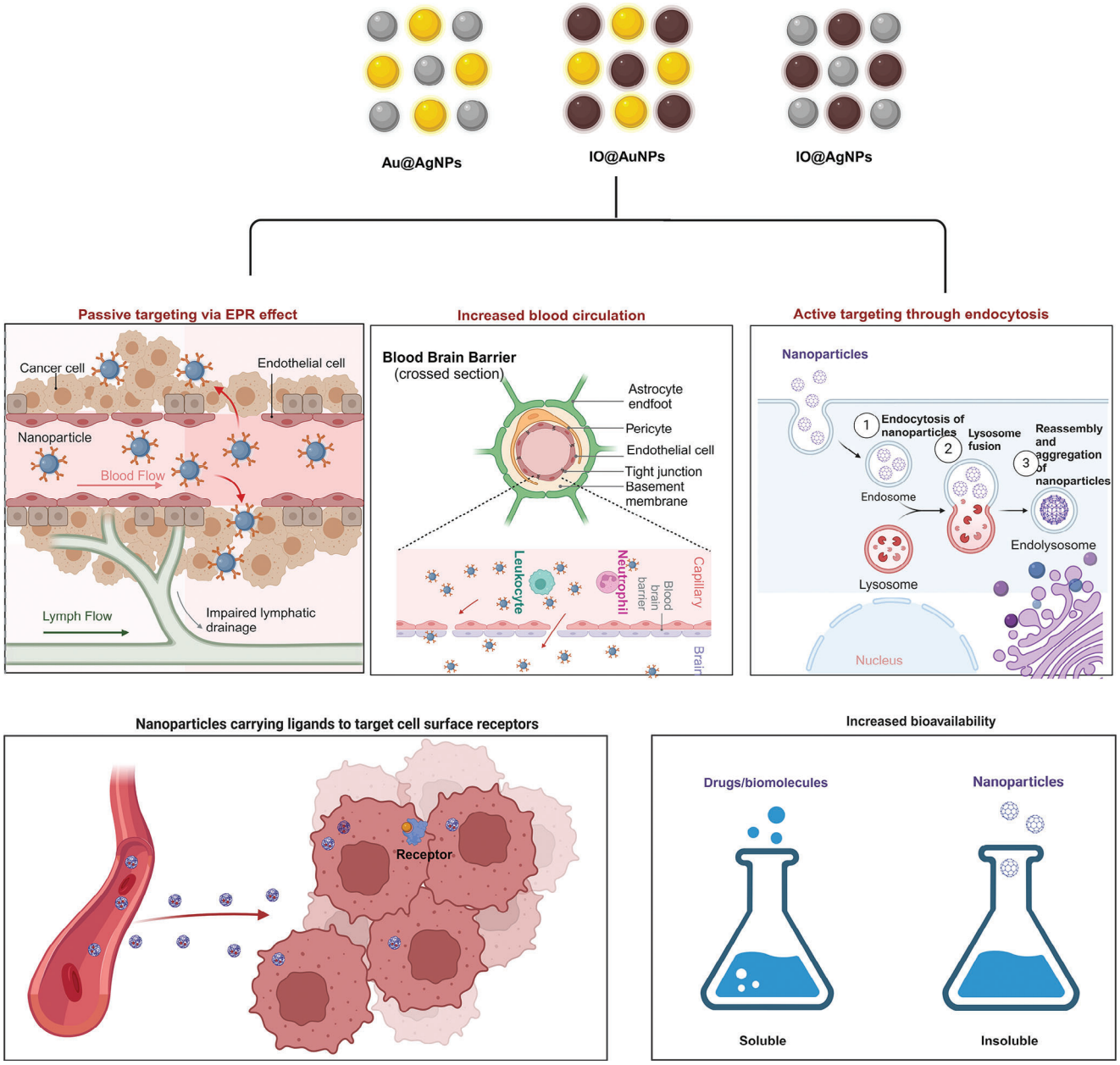

Figure 15. Schematic representation of the advantages of utilizing hybrid metal nanoparticles (Au@AgNPs, IO@AuNPs, IO@AgNPs) in cancer therapy. These nanoparticles enhance therapeutic outcomes through passive targeting via the enhanced permeability and retention (EPR) effect, increased blood circulation, and active targeting via endocytosis. The use of ligands on nanoparticles facilitates specific targeting to cancer cell surface receptors, while the nanoparticles also improve bioavailability of therapeutic agents, providing greater efficacy compared to conventional drug delivery methods. Image created using BioRender (http://biorender.com).

be caused owing to the extra freedom introduced in bimetallic nanoparticles (BNPs). These combined metals in the hybrid nanoparticles are often advantageous over monometallic nanoparticles and produce NPs with high therapeutic efficacy by active targeting (**Figure 15**). Precisely developing BNPs by considering composition, configuration, and/or surface modification, stability can be achieved, and thus additional investigations are strongly warranted to explicate BNPs application in medicine, notably in oncotherapeutics.[400–404] The BNPs in conjugation drugs are often promising due to improved drug stability, retention in their body, improved cellular uptake, and direct targeting to cancer cells. Studies have also demonstrated that BNPs can improve drug loading efficiency, especially in acidic pH, reminiscent of the tumor environment.[405–408]

Apart from this, BNP systems adapt other drug-loading mechanisms such as temperature and enzyme-trigged drug desorption.[407] For instance, Pt and AuNPs can be synthesized using chemical reduction or green chemistry methods. However, synthesizing bi-metallic-DOX nanocomposite delivery systems using sodium borohydride as the reducing agent is often pricey

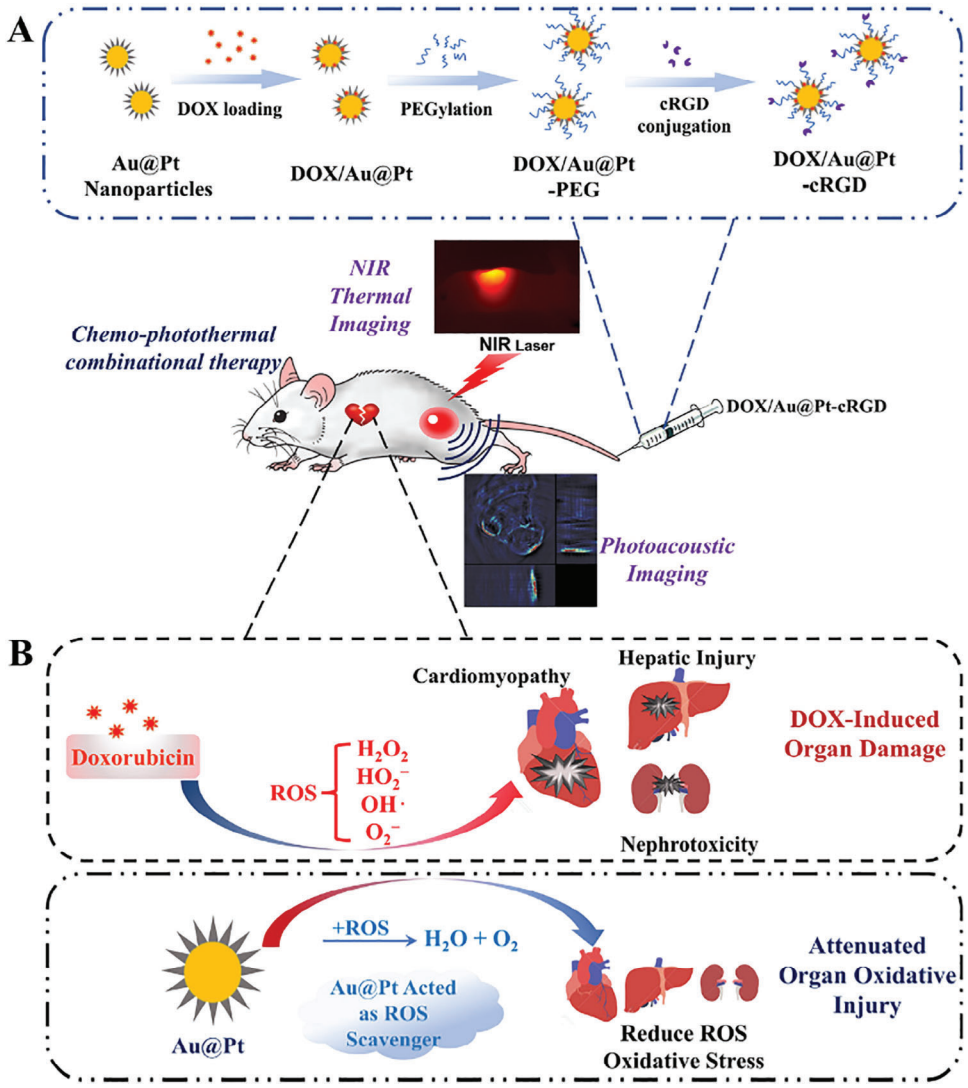

Figure 16. Schematic illustrations of a) the synthesis of DOX/Au@Pt-cRGD, and b) ROS scavenging by catalyzing the platinum shell while attenuating DOX-induced organ oxidative injury were adapted from ref. [418] with permission.

and harmful. Therefore, adopting an eco-friendly approach encourages phytochemicals in the plant extract to be used as reducing and stabilizing agents that provide less cost-effective, simple, facile, and eco-friendly NPs.[409–412] In addition, plant-derived NPs have demonstrated enhanced therapeutic efficacy compared to those prepared using chemical reductant methods.[413] To avoid the interaction of nanoparticles with biological barriers and to increase the blood circulation time of DOX, recognition by the reticuloendothelial system (RES) must be prevented.[414] Therefore, PEGylation is used in smart delivery platforms as they possess stealth properties due to their ability to form a stabilizing hydration shell around the nanostructure to enhance DOX activity.[415] By knowing its advantageous properties, recently innovative PEG-modified Au-Pd nanodendrites were approved by the FDA to carry DOX[407] resulting in enhanced DOX loading onto dendritic-shaped BNPs.[416]

A temperature-controlled release of a DNA-coated NIR light-responsive drug delivery platform was synthesized based on Au-Ag NRs. In this study, researchers attached DNA (sgc8c) to recognize specific tumors in Au-Ag NR-based nanogels to release the drug rapidly onto the target site. Upon NIR exposure, the drug DOX can be released rapidly and have an improved tumor-killing effect.[417] Furthermore, BNPs become especially important because they can be used for diagnosis and treatment. For example, cRGD-modified DOX-loaded Au@PtNPs (DOX/Au@Pt-cRGD) have been used as an exceptional chemo-photothermal co-therapy that targets only diseased cells, as well as fluorescence imaging because of their optical features (**Figure 16**).[418] The synthesis and treatment of combined Ag3AuTrp1:2NPs in tumor mice increased NPs accumulation, which was approximately equal to 2.3% ID g^{-1} at 30 minutes post administration, even though only 1% of total administration reached the solid tumor. The increased accumulation of BNPs at the target site increased apoptosis by increasing ROS-induced oxidative stress.[1] To improve the individual distinct properties of AgNPs and IONPs and to encourage synergistic action, smaller and spherical-sized

IONPs, and AgNPs are combined as one hybrid nanostructure to modulate Ehrlich carcinoma (EC). This work demonstrated that IO@AgNPs increased radiosensitivity of solid EC relative to IONPs treatment by decreasing cytoprotective autophagy and increasing calcium-dependent apoptosis.[419,420]

Overall, BNPs have shown numerous potentials in cancer therapy, but many features remain unknown. So far, it is well known that BNPs often exhibit significant anticancer activity and high sensitivity, allowing them to operate as enzymes in the TME. Furthermore, they are regarded as extremely novel tactics that can be employed synergistically in drug delivery and cancer detection, monitoring tumor growth and automatically adjusting the level of treatment. Therefore, BNPs are considered smart nano-delivery platforms as they can perform multifunctional roles such as sensing, imaging, drug loading, catalytic performance, and photothermal properties.[421]

5.3. Toxicity and Biocompatibility in Cancer Applications

Metal nanoparticles may typically overcome the disadvantages of conventional chemotherapy by enabling the targeted and regulated release of anticancer medicines. Therefore, their use as drug carriers is encouraged. Among various types of metal nanoparticles, noble metals are more advantageous over other nanoparticles due to their high stability, biocompatibility, and possible large-scale production for improved biomedical applications.[422] Despite their broad applications, metal nanoparticles still need to improve in various aspects such as toxicity, size, uptake, and stability. There are various ways to improve their biocompatibility and to decrease toxicity to nearby tissues, including functionalization of targeting moieties, coating of nanoparticles using biocompatible layers, and synthesizing BNPs to enhance in vivo stability, increase drug accumulation in the tumor site, improved therapeutic effectiveness of carried drugs, and reduce systemic toxicity. Apart from this, depending upon the type of BNPs synthesis, above claim can be largely varied. To attain more biocompatibility and less toxicity of bimetallic nanoparticles, the green synthesis method is a more promising approach compared to other methods. Additionally, bimetallic nanoparticles are well known to exhibit synergistic effects in various biological applications, including medicine. In this section, we will be discussing the research work done to improve their biocompatibility and toxicity to normal cells with improved anticancer effects.

A proper functionalization of nanoparticles could enhance the interaction of surrounding environments for effective cancer therapy. For instance, functionalization of nanoparticles with ligands enhanced affinity towards proteins and cell surface molecules. In a study, displacement of the green fluorescence protein (GFP) from the surface of AuNPs occurs when cells added to emit fluorescence is entirely dependent on the nanoparticle-cell affinity, which can be adjusted by slight modification on the head of ligands.[423] Further, several studies confirmed using a biocompatible layer to overcome the drawbacks of uncoated NPs. Recently, coatings have been used to stabilize their physicochemical and biological properties. For instance, folate is well suitable as a biological agent due to its stability, non-immunogenicity, and specificity to cancer cells, etc.; Kefayat et al. demonstrated folate and BSA-coated AuNPs accumulated ≈2.5 times higher in C6 glioma tumor cells than that of normal cells indicating their strongest targeting effect.[424–426] The exhibition of cytotoxicity to cancer cells induced by either nanoparticles or coatings mainly depends on several parameters such as the type of the nanoparticles, size, shape, treatment time, and also types of cell line.[427–430] For example, 10, 25, and 50 μg mL^{-1} IONPs treated to A-549 cells exhibited concentration-dependent cell death.[431] In another study, IONPs coated with the bipolar surfactant such as tetramethylammonium 11-aminoundecanoate at low concentrations, i.e., 0.1 to 10 μg mL^{-1} did not show toxic effects on HeLa cells indicating that the anticancer activity was highly dependent on the concentration of NPs.[432] In this line, researchers have generated stable, homogenous, and thin layers of dextran-coated IONP solution (D-MNPs) or suspensions that demonstrated time-dependent biocompatibility to HeLa cells.

IONPs@AgNPs showed increased cytotoxicity than IONPs because AgNPs increased the toxicity to IO. This enhanced activity is due to the assembly of ion chains in the cell membrane's enhanced affinity for nanoparticles, which resulted in the downregulation of transcriptional regulation and protein synthesis, causing cell death.[433] In a recent study, researchers targeted DNA damage by applying combinational therapy using IO-Ag after a low radiotherapy dose. This resulted in better performance than IONPs and overcame the toxicity of high doses of radiation therapy by increasing the cytotoxic effect of the Ehrlich model.[420] Additionally, chemo-photothermal combinational therapy synthesized multifunctional Au@Pt nanoparticles loaded DOX-targeted cancer cells while reducing systemic toxicity response by decreasing ROS generation.[418]

5.4. Immunogenicity and Clearance Challenges in Cancer Therapy

Recently, immunotherapy has gained popularity and is regarded as one of the most successful cancer treatment strategies because cancer cells induce immunogenic cell death (ICD) by activating the immune system and transforming it into self-vaccines. On the other hand, immunogenicity is largely decreased when there is frequent exposure to phosphatidylserine (PS), an immunosuppressive signal on the cancer cells surface used to reduce antitumor immunity. Therefore, studies focused on enhancing the antitumor activity by using nanoparticles to induce ICD (**Figure 17**).

Recently, bimetallic metal-containing frameworks (MOF) nanoparticles containing Gd3+ and Zn2+ (Gd-MOF-5) have been synthesized to modulate cell signaling by downregulating PS externalization and upregulating ICD, therefore stimulating immune response for targeted cancer immunotherapy (**Figure 18**). In a different approach, coating the nanoparticles with polymer improved immunotherapeutic efficacy. For instance, polymer-stabilized AuNPs (P-Au-NPs) have several advantages, including prolonged stability of AuNPs, modified solubility, enhanced outer surface hydrophilicity, reduced immunogenicity, and increased biocompatibility.[435] Additionally, biocompatible polymers such as poly (ethylene glycol), heparin, hyaluronic

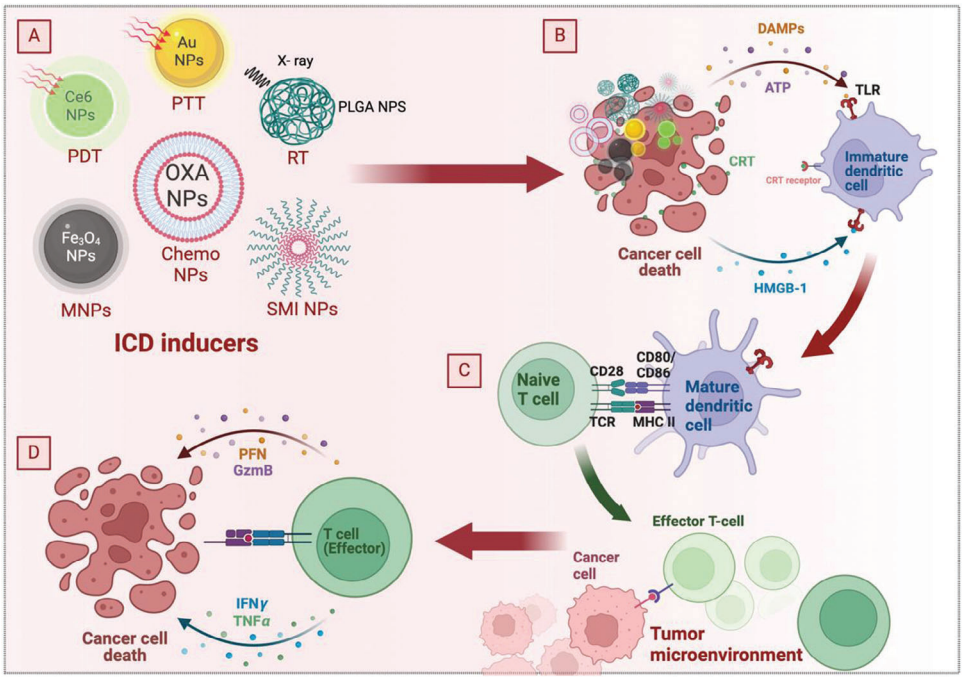

Figure 17. Engineered nanomedicines to trigger immunogenic cell death (ICD) of cancer cells using various approaches were adapted from ref. [434] with permission. Copyright 2024, The authors, Elsevier B.V., on behalf of the Chinese Pharmaceutical Association and Institute of Materia, Chinese Academy of Medical Sciences.

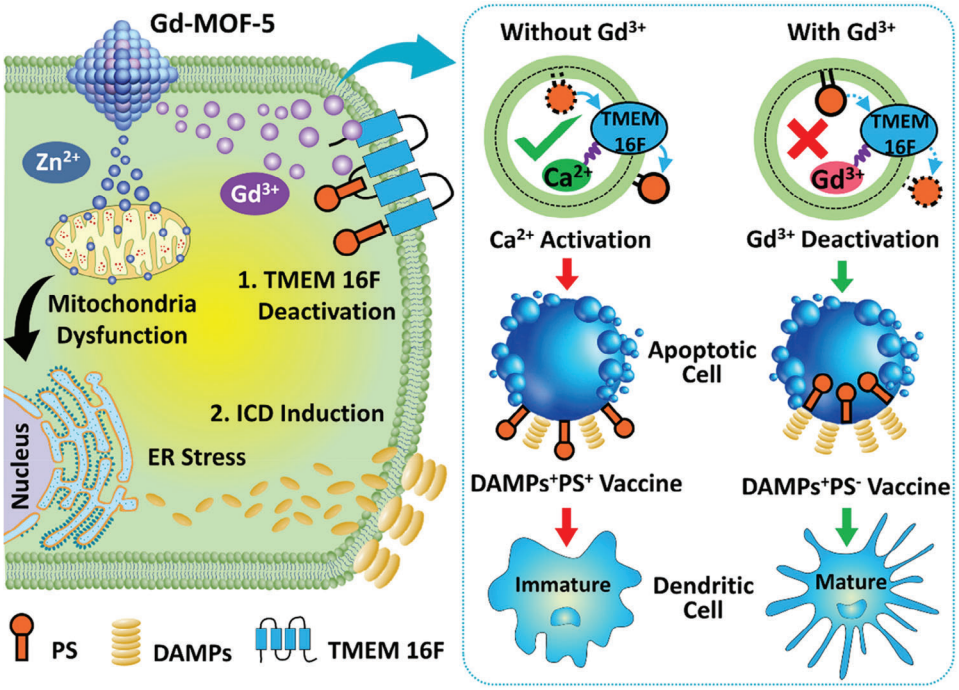

Figure 18. Illustration of the Gd-MOF-5 nanoparticles to modulate immunosuppressive PS and immunostimulatory ICD signals was adapted from ref. [443] with permission. Copyright 2021, Elsevier Ltd.

acid, chitosan, polystyrene sulfonate, polyethyleneimine, and xanthum gum can be used in the surface functionalization of AuNPs to increase the therapeutic efficacy of NPs and payload and to increase long systemic circulation paying the way to use AuNPs effectively in cancer therapy.[436] PEG can be used as it possesses unique characteristics such as biocompatibility and may induce immune reactions upon simultaneous exposure, resulting in an "accelerated blood clearance effect." Using carbohydrates such as chitosan/alginate complex after surface modification such as sulfation and acetylation enhances biocompatibility and anti-cancer effects.[437–439] In another study, glycosylation of AuNPs increased circulation times by decreasing clearance rate and nanoparticle toxicity and by targeting glycan-responsive receptors.[440,441] Further, other nanoparticles, such as magnetic nanoparticles, have also been demonstrated to enhance the circulation times of nanoparticles in vivo.[442] Despite ways available to increase their immunogenicity and clearance, most of the studies remain in the preliminary stage, and therefore, challenges need to be addressed in human patients, including toxicity, stability, and clinical translation.

5.5. Strategies for Mitigating Off-Target Effects in Cancer Therapy

Despite the successful application of metal nanoparticles in cancer therapy, more challenges still need to be addressed. Generally speaking, nano-carriers are bigger than smaller molecules, and therefore, they can increase the blood circulation period, which leads to enhanced accumulation of nanoparticles in target tumor sites, reduce renal clearance and broad tissue distribution, and promote the penetrability and EPR effect of the tumor. Additionally, metal nanoparticles have been extensively explored due to their varying morphology and size, large surface area to volume ratio, elasticity, biocompatibility, stability, porosity, and inertness. Further, nanoparticles can escape multidrug resistance (MDR) and have the ability to release drugs in a controlled manner.[444,445] In spite of the successful application of metal NPs in cancer therapy, still, their use in clinical trials is still in the preliminary stage. In this section, we will address the various approaches to minimize off-target effects during metallic nanoparticles-based cancer therapies that aid nanoparticles moving forward.

The surface coating of bio-functional inorganic nanoparticles with suitable hydrophilic macromolecules helps in overcoming the drawbacks associated with their use in the medical field. The use of stimulus-responsive approaches, such as pH, temperature, enzymes, light, magnetic, and electric fields, are known to enhance the controlled delivery of drug cargo to the tumor site and reduce the side effects of chemotherapy. For instance, pH-responsive nano-carriers can be synthesized to improve the therapeutic efficacy of drugs. The synthesized nanocarriers are sensitive to pH and help in the disintegration of the nano-carrying drugs in the acidic environment and remain stable in the blood and in the extracellular fluid of normal tissues (pH 7.4), resulting in a reduction of biological toxicity due to off-target distribution. Various nanocarriers such as liposomes, polymeric micelles, and hydrogel often result in a variety of limitations, including poor scalability, premature drug degradation, reduced blood circulation period, slow biodegradation, etc.; however, these can be overcome by using pH-sensitive inorganic NPs. A pH-sensitive carbonate apatite (CA), $(Ca_{10}(PO_4)_{6-x}(CO3)_x(OH)_2$ increased biocompatibility, heterogeneous charge distribution, tunable size, and shape, ability to passively accumulate drug to the tumor site through EPR effect to dissociate tumor completely in the endosomal pH, thus promoting the effective release of drug therapeutics into the cytosol of the cancer cells. Another study used DOX loaded α-ketoglutarate (α-KA) with Fe/Mg-CA induced prolonged blood circulation period, drug distribution at the tumor site indicating that the protein corona and size of α-KA- Fe/Mg-CA NPs aided in the biodistribution of DOX in breast cancer cells.[446] Metal nanoparticles are also advantageous over other nanomaterials as they are flexible in size and surface modification and, therefore, considered an excellent carrier for targeted drug delivery to the nucleus by reducing the risk of off-target effects. In this context, several studies were conducted to demonstrate the effect of encapsulation of metal nanoparticles with hydrophilic groups such as PEG on dispersion, in vivo circulation, stability, and toxicity.[447–449] Alternatively, the use of gold nanoconjugates targeting miRNA has recently been spotlighted for cancer diagnosis and treatment due to their ability to direct targeting and a significant reduction in off-target effects. Gold nanoconjugates are also involved in cancer-related gene regulation through miRNA delivery. Furthermore, PEGylated AuNPs were conjugated with a miR-206 mimic targeted NOTCH 3 gene, causing cell cycle arrest in the G0-G1 phase of breast cancer cells.[450] Overall, studies to minimize off-target effects of metal nanoparticles or bimetallic nanoparticles are in the budding stage, and more studies need to be conducted to better understand and efficiently reduce off-target effects.

6. Recent Advances and Future Directions in Cancer Therapy

So far, we have understood that the landscape of cancer therapy has undergone a profound transformation driven by interdisciplinary research and technological innovations. The field is poised for further evolution, guided by a vision of personalized, precise, and effective treatments. Here, we delve into some of the recent breakthroughs and future directions in cancer therapy, specifically focusing on the transformative potential of metallic nanoparticles.

6.1. Personalized Cancer Treatment

Personalized medicine has emerged as a cornerstone of modern cancer therapy, aiming to tailor treatments to the unique molecular characteristics of individual tumors and patients. Metallic nanoparticles, no doubt, have garnered significant interest in this context due to their tunable properties and multifunctional capabilities, which enable tailored approaches to cancer treatment. In particular, AuNPs have been extensively studied for their ability to target tumor cells while sparing healthy tissues selectively. Functionalizing AuNPs with targeting ligands or antibodies specific to tumor biomarkers allows for precise delivery of therapeutic payloads, such as chemotherapeutic drugs or nucleic acids, to cancerous lesions. Moreover, the optical properties of AuNPs,

particularly their SPR, enable real-time imaging of nanoparticle accumulation in tumors, facilitating the optimization of treatment protocols and monitoring therapeutic responses. Similarly, IONPs have been employed for personalized cancer treatment, particularly in MRI-guided therapy. By functionalizing IONPs with tumor-targeting ligands or responsive moieties, researchers have developed smart nanoplatforms capable of site-specific drug delivery and controlled release within the TME. This approach minimizes off-target effects and enhances therapeutic efficacy by overcoming biological barriers to drug penetration.

6.2. Integration with Cancer Immunotherapy

Cancer immunotherapy has emerged as a paradigm-shifting approach to cancer treatment, harnessing the body's immune system to recognize and eliminate tumor cells. Metallic nanoparticles offer unique opportunities for integration with immunotherapy to enhance therapeutic outcomes and overcome immune evasion mechanisms employed by tumors. One strategy involves utilizing AuNPs as adjuvants for cancer vaccines, leveraging their immunomodulatory properties to enhance antigen presentation and immune cell activation. Functionalizing AuNPs with tumor-associated antigens or immunostimulatory molecules promotes robust antitumor-immune responses, leading to tumor regression and long-term protection against tumor recurrence in preclinical models. Furthermore, nanoparticles can be engineered to modulate immune checkpoint pathways, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), to unleash antitumor immune responses. By conjugating immune checkpoint inhibitors to AuNPs or IONPs, researchers have demonstrated synergistic effects with conventional immunotherapies, resulting in enhanced tumor infiltration by cytotoxic T cells and improved overall survival rates in animal models.

6.3. Emerging Trends and Technologies in Cancer Therapy

The future of cancer therapy is shaped by emerging technologies and innovative approaches that leverage the unique properties of metallic nanoparticles. One such trend is the development of multifunctional nanoparticles capable of simultaneous imaging and therapy, enabling real-time monitoring of treatment responses and personalized treatment regimens. For instance, theranostic nanoparticles, composed of AuNPs or IONPs loaded with therapeutic payloads and imaging agents, enable non-invasive visualization of tumor lesions and targeted delivery of therapeutic agents to cancerous tissues. By integrating diagnostic capabilities with therapeutic interventions, theranostic nanoparticles facilitate early detection of treatment response and guide treatment decisions based on individual patient characteristics. Moreover, integrating artificial intelligence (AI) and machine learning algorithms with nanoparticle-based therapeutics holds promise for predictive modeling and treatment optimization. By analyzing large datasets of patient demographics, molecular profiles, and treatment outcomes, AI-driven approaches can identify predictive biomarkers, optimize treatment regimens, and guide personalized treatment decisions tailored to individual patient needs. Additionally, advancements in nanoparticle fabrication techniques, such as 3D printing and microfluidic synthesis, enable precise control over nanoparticle properties and characteristics, leading to enhanced therapeutic efficacy and biocompatibility. By engineering nanoparticles with tailored physicochemical properties, researchers can optimize drug loading capacities, improve targeting specificity, and minimize off-target effects, enhancing therapeutic outcomes and patient safety. As we navigate toward the future of cancer therapy, collaborative efforts between researchers, clinicians, industry partners, and regulatory agencies are crucial to translating these innovative technologies into clinical practice and improving patient outcomes in the fight against cancer.

7. Conclusion

The comprehensive research reviewed highlights the significant potential of gold, silver, and IONPs in advancing cancer therapy. These nanoparticles offer a diverse approach to cancer treatment by leveraging their unique physicochemical properties and functional versatility to address key challenges in oncology. AuNPs, with their biocompatibility, tunable surface chemistry, and distinctive optical properties, have emerged as powerful tools for cancer diagnosis, imaging, and therapy. From targeted drug delivery to photothermal ablation, AuNPs have demonstrated remarkable efficacy in preclinical and clinical settings, paving the way for personalized and precise cancer treatments. AgNPs, renowned for their antimicrobial properties, exhibit intriguing potential in cancer therapy through mechanisms such as apoptosis induction, angiogenesis inhibition, and synergistic interactions with conventional treatments. By utilizing the unique properties of AgNPs, researchers have developed innovative strategies to enhance treatment efficacy and overcome resistance mechanisms in cancer. IONPs, with their magnetic properties and biocompatibility, offer unique opportunities for cancer imaging, targeted drug delivery, and magnetic hyperthermia therapy. Integrating IONPs with imaging modalities such as MRI enables real-time monitoring of treatment responses and disease progression, facilitating personalized treatment regimens tailored to individual patient needs.

Looking ahead, future research directions in the field of nanoparticle-based cancer therapy include several things. Continued efforts to optimize nanoparticle design, synthesis, and functionalization to enhance their biocompatibility, stability, and targeting specificity. Further exploration of the synergistic effects of combining metallic nanoparticles with cancer immunotherapy, focusing on modulating immune responses and overcoming immunosuppressive barriers in the TME. Advancements in developing theranostic nanoparticles capable of simultaneous imaging and therapy enable real-time monitoring of treatment responses and personalized treatment regimens. Accelerating the translation of nanoparticle-based cancer therapies from preclinical studies to clinical trials, focusing on optimizing treatment protocols, evaluating safety profiles, and demonstrating therapeutic efficacy in patient populations. Continued exploration of novel nanoparticle-based therapies, such as exosome-based drug delivery systems, bioinspired nanoparticles, and stimuli-responsive nanocarriers, for targeted and personalized cancer treatment.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

P.S. conceived and designed the study, contributing significantly to its overall direction, framework, and writing. All authors collaboratively wrote, reviewed, and revised the manuscript. Additionally, all authors have read the final version of the manuscript and agreed to its submission.

Keywords

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