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Review

Conjugated Nanoparticles for Solid Tumor Theranostics: Unraveling the Interplay of Known and Unknown Factors

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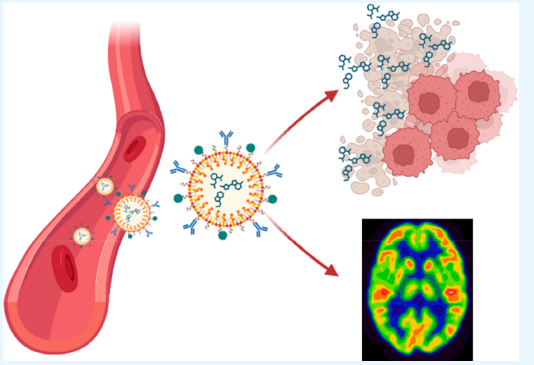
ABSTRACT: Cancer diagnoses have been increasing worldwide, and solid tumors are among the leading contributors to patient mortality, creating an enormous burden on the global healthcare system. Cancer is responsible for around 10.3 million deaths worldwide. Solid tumors are one of the most prevalent cancers observed in recent times. On the other hand, early diagnosis is a significant challenge that could save a person's life. Treatment with existing methods has pitfalls that limit the successful elimination of the disorder. Though nanoparticle-based imaging and therapeutics have shown a significant impact in healthcare, current methodologies for solid tumor treatment are insufficient. There are multiple complications associated with the diagnosis and management of solid tumors as well. Recently, surface-conjugated nanoparticles such as lipid nanoparticles, metallic nanoparticles, and quantum dots have shown positive results in solid tumor diagnostics and therapeutics in preclinical models. Other nanotheranostic material platforms such as plasmonic theranostics, magnetotheranostics, hybrid nanotheranostics, and graphene theranostics have also been explored. These nanoparticle theranostics ensure the appropriate targeting of tumors along with selective delivery of cargos (both imaging and therapeutic probes) without affecting the surrounding healthy tissues. Though they have multiple applications, nanoparticles still possess numerous limitations that need to be addressed in order to be fully utilized in the clinic. In this review, we outline the importance of materials and design strategies used to engineer nanoparticles in the treatment and diagnosis of solid tumors and how effectively each method overcomes the drawbacks of the current techniques. We also highlight the gaps in each material platform and how design considerations can address their limitations in future research directions.



INTRODUCTION

Cancer is considered the most lethal form of human malignancy and the leading cause of mortality globally.[1−3] The National Cancer Institute defined a solid tumor as an abnormal tissue mass devoid of liquid or cysts, such as lymphomas, carcinomas, and sarcomas, that could be malignant or benign.[4] However, the tumor is not always associated with cancer. At the same time, the majority of malignancies become solid tumors in the tissue where they first arise, such as the bladder, breast, cervical colon, endometrial, kidney, liver, lung, melanoma, mesothelioma, ovary, prostate, pancreas, skin, and thyroid.[5] Similar to normal tissue, tumor neovascularization may involve angiogenesis, migration, immunosuppression, cell proliferation, invasion, vasculogenesis, and metastasis. The tumor vasculature is quite different from the vasculature of normal tissues both functionally and morphologically. Small tumors smaller than 2 mm in diameter are mostly perfused by nearby host tissues.[6] In cases when a solid tumor reaches a threshold size, diffusion does not provide access to the inner tumor microenvironment. Therefore, the size of a tumor plays a significant role in dependent drug delivery mechanisms.[7,8] Tumor growth and expansion are closely associated with newly emerging microvessels, implying that microcirculation is critical in the development, diagnosis, metastasis, and treatment of solid tumors.[9,10] Also, blood flow to solid tumors is crucial in delivering chemotherapeutic agents to the tumor site.[11,12] Nevertheless, compared to normal tissues, tumor tissues exhibit comparable arterial pressure but lower venous pressure. This pressure gradient leads to blood flow, which is insignificant in the core portion of a tumor but higher in the peripheral compartment.[13] Moreover, the blood viscosity in the tumor microenvironment is higher than in the normal tissues, given the presence of tumor cells and more

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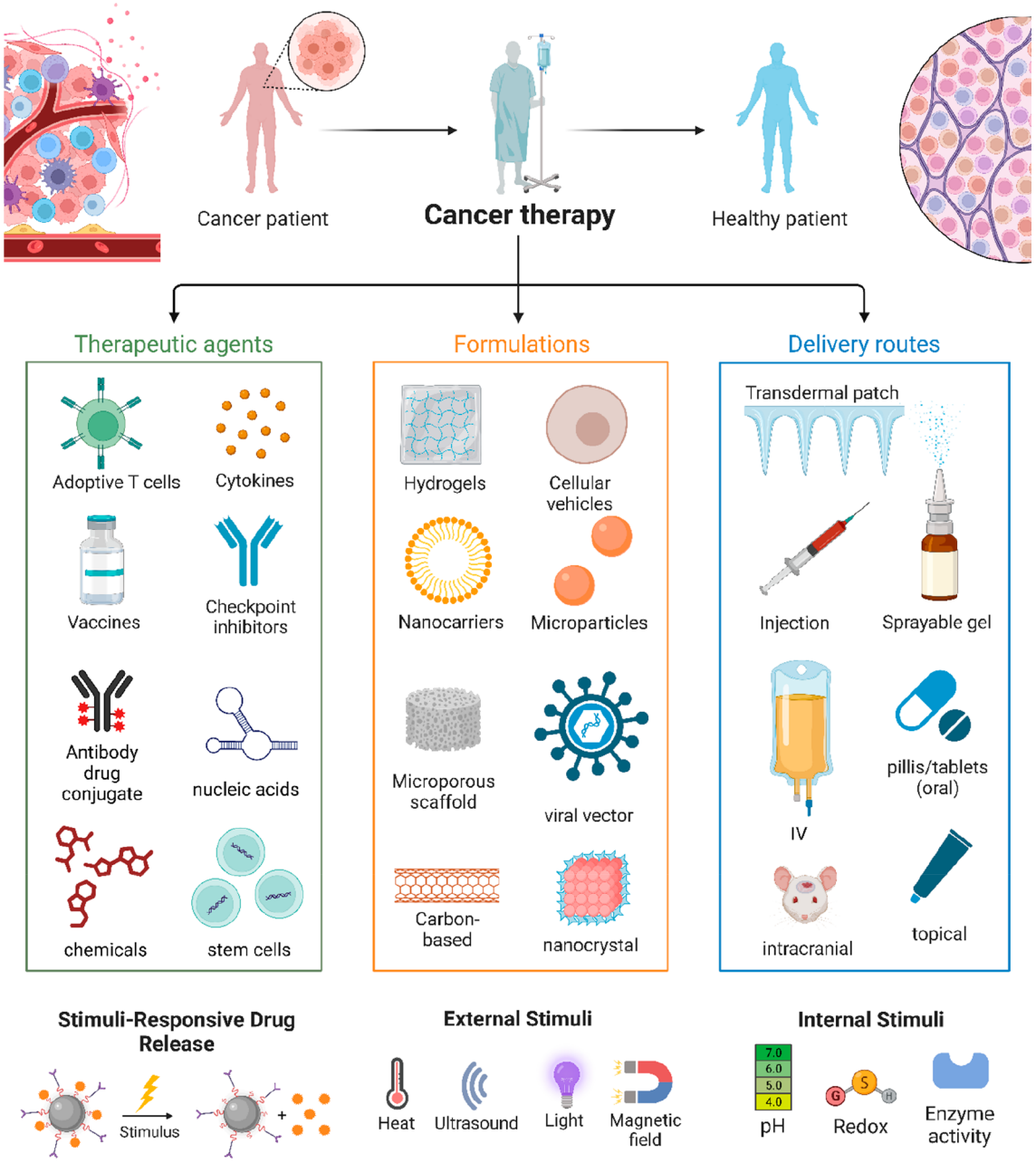

Figure 1. Cancer therapy helps the patient recover from the life-threatening disease. It includes multiple sectors such as therapeutic agents, formulations, and delivery routes. Therapeutic agents enrolled in cancer management are adoptive T cells, cytokines, vaccines, stem cells, chemicals, and many more. Similarly, formulation includes hydrogels, nanocrystals, viral vectors, nanocarriers, etc. The different delivery routes include injection, pills, intracranial, IV, and many more. Produced in Biorender.

giant molecules like protein, causing an increase in the flow resistance in tumor microcirculation leading to compromised drug bioavailability at the target site. This justifies the heterogeneous blood flow within a solid tumor, which is lower within the tumor mass when compared with the marginal cells, leading to variable drug bioavailability and, thus, lesser therapeutic efficiency.

Current cancer statistics show that solid tumors comprise around 85% of all malignancies worldwide.[14] The FDA has approved numerous monoclonal antibodies against immunological checkpoints PD-1, PD-L1, and CTLA-4 for cancer treatments, out of which a small number of 25% are employed as first-line treatment for solid tumors.[15] This deficit may be attributable to the obstacles in obtaining enough exposure in the tumor microenvironment of solid tumors. The efficacy of cancer treatment in a solid tumor is contingent on the targeted and effective delivery of the therapeutic cargos to the tumor cells. Cases with inadequate drug delivery to the target site could develop residual tumor cells, leading to relapse and regrowth of tumors and possibly the buildout of resistant tumor cells.

Carcinoma is a broader classification of solid tumors, including breast, prostate, and colon cancer. Statistics have shown that invasive ductal carcinoma accounts for more than 80% of all breast cancer diagnoses and is the leading cause of cancer-related mortality in females. On the other hand, in the male population, prostate cancer is the most common malignancy that accounts for the fifth most significant cause

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GBD level 2 cause of disease or injury	Absolute DALYs, millions (95% UI)	Global ranking	Low SDI ranking	Low-middle SDI ranking	Middle SDI ranking	High-middle SDI ranking	High SDI ranking
Cardiovascular diseases	393 (368-417)	1	6	1	1	1	2
Total cancers (excluding NMSC)	**249 (234-263)**	**2**	**10**	**4**	**2**	**2**	**1**
Maternal and neonatal disorders	199 (172-232)	3	1	2	7	15	17
Other noncommunicable diseases	153 (124-187)	4	5	5	5	5	6
Respiratory infections and tuberculosis	153 (137-172)	5	2	3	9	14	16
Musculoskeletal disorders	150 (109-198)	6	18	9	3	3	3
Mental disorders	125 (93.0-163.0)	7	11	8	6	4	4
Diabetes and kidney diseases	113 (99.3-128.0)	8	17	11	4	8	7
Unintentional injuries	104 (88.9-120.0)	9	12	10	11	7	8
Chronic respiratory diseases	104 (94.8-112.0)	10	16	7	8	9	9
Neurological disorders	97.7 (55.9-159.0)	11	19	14	10	6	5
Enteric infections	96.8 (79.2-120)	12	3	6	18	20	19
Digestive diseases	89.0 (81.4-97.6)	13	13	12	13	10	11
Transport injuries	77.6 (69.2-85.5)	14	15	13	12	12	15
Self-harm and interpersonal violence	67.9 (63.4-72.9)	15	14	15	15	13	13
Sense organ diseases	66.1 (45.1-93.0)	16	20	19	14	11	12
Neglected tropical diseases and malaria	62.9 (38.6-96.0)	17	4	18	20	22	22
HIV/AIDS and sexually transmitted infections	56.2 (48.4-67.0)	18	8	17	16	19	20
Other infectious diseases	51.4 (40.7-66.0)	19	7	20	22	21	21
Nutritional deficiencies	49.8 (36.9-65.8)	20	9	16	19	18	18
Skin and subcutaneous diseases	42.9 (28.6-63.4)	21	21	21	17	17	14
Substance use disorders	35.1 (28.2-43.0)	22	22	22	21	16	10

Figure 2. Ranking of total cancer absolute disability-adjusted life years (DALYs) in 2019 among the 22 level 2 categories of disease in the Global Burden of Disease (GBD) study by Quintile of Sociodemographic Index (SDI) total cancers, excluding nonmelanoma skin cancer. The GBD study organized diseases and injuries into a hierarchy that was mutually exclusive and collectively exhaustive. More details of this hierarchy were previously published. Colors represent the ranking of the cause within a given location group (e.g., high SDI quintile) from red (highest ranking) to green (lowest ranking). The other noncommunicable diseases include congenital birth defects; urinary diseases and male infertility; gynecological diseases; hemoglobinopathies and hemolytic anemias; endocrine, metabolic, blood, and immune disorders; oral disorders; and sudden infant death syndrome. The other infectious diseases include meningitis; encephalitis; diphtheria; whooping cough; tetanus; measles; varicella and herpes zoster; acute hepatitis; and other unspecified infectious diseases. NMSC indicates nonmelanoma skin cancer; UI, uncertainty interval. Adopted under CCBY4 from ref 3. Copyright (2022) JAMA Oncology.

of mortality among men. Colon cancer is also the leading cause of mortality in the US.[16] The statistics show the urgency to immediately develop novel methods and tools to mitigate solid tumors. Nanotheranostic approaches involve using nanoparticles (NPs) for diagnostic and therapeutic purposes.[17−19] Nanomedicine with theranostic capabilities can circulate through the body, avoid the host's defense, and deliver drugs and diagnostic agents to the targeted site for cellular and molecular-level diagnosis and treatment.[20−22] The therapeutic and diagnostic agents are combined into a single theranostic platform that can be linked to a biological ligand for targeted delivery. Nanotheranostics also offer responsive drug release, synergistic and combined therapy, codelivery of siRNA, multiple therapeutic approaches, oral administration, delivery to the brain through the blood−brain barrier, and protection from intracellular autophagy. Refer to Figure 1 for the basic understanding of the application of nanoparticles in both diagnosis and treatment. Exosome-based delivery systems are also under different stages of development for cancer treatment.[23,24]

The use of nanotheranostics in solid tumors, including drugs undergoing preclinical and clinical trials as well as current challenges and future issues, will be highlighted in this review. Arranja et al. presented the fundamental concepts behind the utilization of nanoparticles for targeting tumors, emphasizing the advantages associated with incorporating imaging techniques to identify suitable patients and customize nanomedicine therapies.[25] In addition, Siddique et al. explored the latest breakthroughs in cancer theranostics facilitated by functionalized nanoparticles. By gaining insights into the ongoing advancements and progress in nanoparticle-based cancer theranostics, the authors cover the forthcoming obstacles and prospects in this innovative approach to treating cancer.[26] However, this review delves into a specific aspect of nanothermostics in managing solid tumors using various materials. This review stands out from previous reviews in terms of its narrowed scope, innovative methodologies, incorporation of recent literature, and consideration of alternative viewpoints. By leveraging these distinguishing factors, this review aims to contribute new perspectives, deepen the understanding, and advance the knowledge within the field.

EPIDEMIOLOGY OF SOLID TUMORS

According to a Global Burden Disease study, the cancer burden has expanded most in the low and low−middle social-demographic index (SDI) quintiles during the past decade (Figure 2). The findings of this thorough analysis indicate that

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the worldwide cancer burden is large and expanding, with burden varying by SDI. These findings give thorough and comparable estimates that have the potential to aid global efforts toward equitable cancer control. Such estimations are critical for enhancing global cancer outcome equity and attaining important SDG targets for cancer and other noncommunicable disease burden reduction.[3]

The prevalence of one or more types of cancer has burdened every nation in the world. According to GLOBOCAN 2020, there were 10.3 million cancer-related deaths and 19.3 million new disease cases worldwide.[27] Of these instances, female breast cancer (11.7%), lung cancer (11.4%), and prostate cancer (7.3%) were the most frequently diagnosed cancers worldwide.[27] The combined cancer mortality shows that of all cancer-related fatalities lung cancer (18%), liver cancer (8.3%), stomach cancer (7.7%), and breast cancer (6.9%) were the leading causes of cancer death. According to data on cancer incidence and mortality by sex, the most common cancers found in men are lung (14.3%), prostate (14.1%), non-melanoma skin (7.2%), and stomach (7.1%) cancers.[28] In contrast, the most common cancers found in women are breast (24.5%), lung (8.4%), and cervix (6.5%) cancers.[29]

Cancer, behind cardiovascular disorders, is the second most significant cause of disease-associated mortality worldwide.[30] A complete investigation of cancer related to the environment, social, and economic conditions and hereditary factors can be done using country-specific counts and analyses of cancer incidences and deaths.[29] The country-specific authorities provide information on specific regional efforts to avoid or control cancer programs and more comprehensive data on regional cancer incidences and mortality. The country-specific examination of cancer burden also emphasizes prioritizing regional and national efforts to prevent cancer based on the cancer patterns seen.[29]

CHALLENGES IN THE MANAGEMENT OF SOLID TUMORS

Treating solid tumors is a challenging task for the healthcare system. Current diagnoses and treatments, even the standard ones, are loaded with pitfalls. In this era, developing advanced formulations to cope with challenges is crucial. However, many researchers are working to compensate for the complexity of solid tumor malignancies.[31] Early diagnosis is crucial to increasing the probability and ease of treatment. The development of technology has brought new advances in diagnostic approaches. For instance, liquid biopsies are a widely accepted technique for diagnosis. It incorporates cDNA, which targets genomic alteration and mutation hotspots to detect the cancerous mass.[32] It was noted that genomic dissimilarities are rare in pediatric patients, which complicates the detection process.[33] Other diagnostic strategies employ the use of invasive techniques, which patients and physicians do not prefer. Biopsies, a gold standard diagnostic approach, are especially susceptible to producing false-positive as well as false-negative results. They might consider low-grade fibromyxoid sarcoma as benign when it is in fact a malignant form.[34] In comparison, benign lesions such as fibrous histiocytoma, cellular benign fibrous histiocytoma, and many more are mistaken for malignant forms of tumors.[34,35] Radiation diagnostics such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans are involved in the diagnosis. MRI is widely used but is not preferred for detecting retroperitoneal sarcoma.[36] All these hurdles demand the development of novel approaches to attain better diagnostic characteristics.

Even after a successful diagnosis, treating cancer is a significant obstacle. Resection and other surgical interventions are standard methodologies for treating solid tumors. However, it was noted that in the resection of neuroblastoma the chances of complications such as infiltration of the growth pattern are observed, reducing its usage as a therapeutic measure.[37] USFDA has approved "rituximab" as an effective antineuroblastoma agent; many others are under clinical supervision. Although selective and compelling, add-on studies are required to claim patient selection for any specific immune-based therapy.[38] Another widely used method is central venous catheters (CVCs), especially in pediatric patients. The probability of consequences could be as high as 40%.[39] Problems can also occur during the operation, such as life-threatening arrhythmia, thoracic duct damage, nerve damage, arterial puncture, and even fatality.[40] Hyperthermic intraperitoneal chemotherapy (HIPEC) and combination therapy of HIPEC and cytoreductive studies are widely studied in many clinical trials, especially for treating solid tumors in ovarian cancer. A study concluded that more than 95% of patients (n = 245) were observed to have at least a single adverse effect after 6 weeks of chemotherapy. It was also observed that patients with only surgery or surgery along with HIPEC had an adverse diagnosis of grade 3 or grade 4 by 25% and 27%, respectively.[41]

FUNCTIONAL MATERIAL PLATFORMS IN CANCER THERANOSTICS

The enormous hurdles in the management of solid tumors, in the fields of both diagnosis and treatment, demand an innovative approach to dealing with the disease. Nanotheranostics research is an emerging area that ensures effective diagnosis and targeted therapy of the moiety. It promises a minimum adverse reaction and maximum efficacy of the formulation. The primary building blocks of nanotheranostics are NPs, which include aptamers, DNA nanostructures, metallic nanoparticles (MNPs) such as gold and silver, dendrimers and copolymer-based or lipid-based NPs, magnetic NPs, iron oxide NPs, mesoporous silica NPs, or quantum dot NPs. NPs have unique attributes, including a high surface-area-to-volume ratio and quantum confinement, allowing for successful modulation in various fields.[42] The following section comprehensively reviews key material platforms used to synthesize nanoparticles for theranostic applications.

Lipid-Based Nanoparticles. Lipid-based nanoparticles involve liposomes, solid−lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), etc.[43,44] Liposomes, composed mainly of biocompatible and biodegradable phospholipids organized in a bilayer structure, are extensively studied nanoparticle drug delivery systems capable of encapsulating both hydrophobic and hydrophilic drugs.[45] Addition of cholesterol to their formulations improves the stability and enhances the permeability of hydrophobic drugs through the bilayer membrane, resulting in different liposome types including multilaminar vesicles (MLVs), large unilamellar vesicles (LUVs), and small unilamellar vesicles (SUVs) with sizes ranging from 0.5 to 100 nm.[46] SLNs are a new colloidal drug delivery system composed of physiological lipids that remain solid at both room and body temperature, with particles ranging in size from 50 to 1000 nm. Solid lipids, including mono-, di-, or triglycerides, fatty acids, and complex

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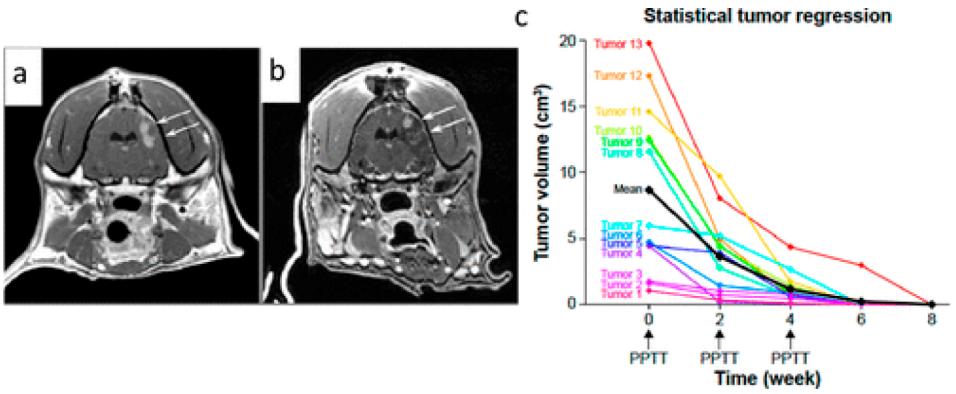

Figure 3. (a–c) Tumor regression in dogs and cats in different organs using Aurolase therapy, a type of plasmonic photothermal therapy using a silica-gold nanoshell. (a, b) Permeability MRI images of a canine brain showing enhancement of a bilobed tumor before and after treatment. (c) Tumor regression curves in mammary glands of 13 cats and dogs following treatment using gold nanorods. Adapted with permission from ref 64. Copyright (2019) American Chemical Society.

glyceride mixtures, form a matrix material for drug encapsulation, stabilized by surfactants or polymers. SLNs provide significant advantages, including site-specific targeting, long-term physical stability, controlled release of both lipophilic and hydrophilic drugs, labile drug protection, low cost, ease of preparation, and low toxicity effects on human granulocytes.[47] However, SLNs have some disadvantages, such as moderate drug-loading capacity and drug expulsion due to crystallization under storage conditions.[48] NLCs, a second generation of lipid-based nanocarriers, are a combination of solid and liquid lipids, developed to overcome SLN limitations. They have higher drug loading capacity and avoid drug expulsion during storage by preventing lipid crystallization. NLCs are composed of glyceryl tricaprylate, ethyl oleate, isopropyl myristate, and glyceryl dioleate, have particle sizes similar to SLNs, can be surface-modified and targeted, and offer controlled drug release. However, they also have disadvantages such as drug expulsion after polymorphic transition and low loading capacity.[49]

Soft Molecule Polymeric Nanoparticles. By combining various functional units with soluble macromolecules using self-assembling copolymers, polymeric NPs can be produced. In the synthesis of polymeric NPs, conventional natural polymers like chitosan, gelatin, albumin, sodium alginate, and poly(lactic-*co*-glycolic acid) (PLGA), as well as synthetic polymers like poly(lactic acid), poly glutamic acid, polyglycolide, polyaspartic acid, and polyanhydride, are frequently used.[49] Practical methods are needed to reduce immunogenicity and antigenicity and to lengthen the residence period and stability inside the biological system for polymeric NPs. Therefore, polyethylene glycol (PEG) is added to nanocarriers to shield the polymeric nanocarrier from steric hindrance and renal clearance. Additionally, physiochemical characteristics like crystallinity, molecular weight, hydrophobicity, and polydispersity index control how quickly the polymeric NPs dissolve and transport drugs.[50] Polymeric NPs are uniquely modified to produce hydrophobic environments to encapsulate hydrophobic medications to the designated target.[51] Nanocapsules, nanospheres, polymeric micelles, drug–polymer conjugates, dendrimers, polymersomes, and polyplexes are examples of polymeric NPs.[52]

Dendrimers have demonstrated great promise as nanocarriers for the delivery of tumor-specific drugs. Dendrimers have a specific architecture and composition, are highly branching, and have a monodispersed weight distribution.[53] Substantial positive charges on dendrimers make them effective transfecting agents, and functional groups on their surfaces enable them to be functionalized with antibodies, peptides, folate, and other targeted compounds.[54] Dendrimers have limitations, including that dendrimers can interact with proteins, organelles, and membranes of nanoscale cells. The lipid bilayer may interact with dendrimers with cationic surface groups, increasing permeability while reducing the integrity.[55,56]

Spheroid nanoplatforms with a hydrophilic shell and a hydrophobic core are known as polymeric micelles. They are more drawn to disease therapies due to their high payload with lower dimensions, thermodynamic stability, and kinetic stability.[57] When used as a three-in-one nanocarrier system in cancer therapy, PEG-poly(lactic acid) micelles can transport hydrophobic medicines, including paclitaxel 17-allyamino-17-demethoxygeldanamycin and rapamycin. In addition, they can be used as a near-infrared (NIR) optical imaging agent due to PEG-*block*-polycaprolactone micelles that are entrapped with the drug carbocyanine.[58] A multipurpose MRI and drug delivery agent are possible when superparamagnetic IONPs and DOX are confined within the core of polymeric micelles.

Drug–polymer conjugates are made by covalent bonding through various chemical methods based on the functional groups of the drug and polymeric carriers involved. The two primary forms of conjugates are protein and drug conjugates with suitable polymers.[59] *N*-(2-Hydroxypropyl) methacrylamide (HPMA) is the most effective polymer for theranostic drug–polymer conjugates. HPMA-based conjugates are favored in theranostics because they are stable, nontoxic, and biocompatible for *in vivo* use.[60,61] Chemical conjugation and copolymerization are the standard ways of functionalizing HPMA copolymers with diagnostic and therapeutic agents.

Lipid-based nanoparticles involve liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), etc.[43] Liposomes, composed mainly of biocompatible and biodegradable phospholipids organized in a bilayer structure, are extensively studied nanoparticle drug delivery systems capable of encapsulating both hydrophobic and hydrophilic drugs. Addition of cholesterol to their formulations improves stability and enhances permeability of hydrophobic drugs through the bilayer membrane, resulting in different liposome types including multilaminar vesicles (MLVs), large uni-

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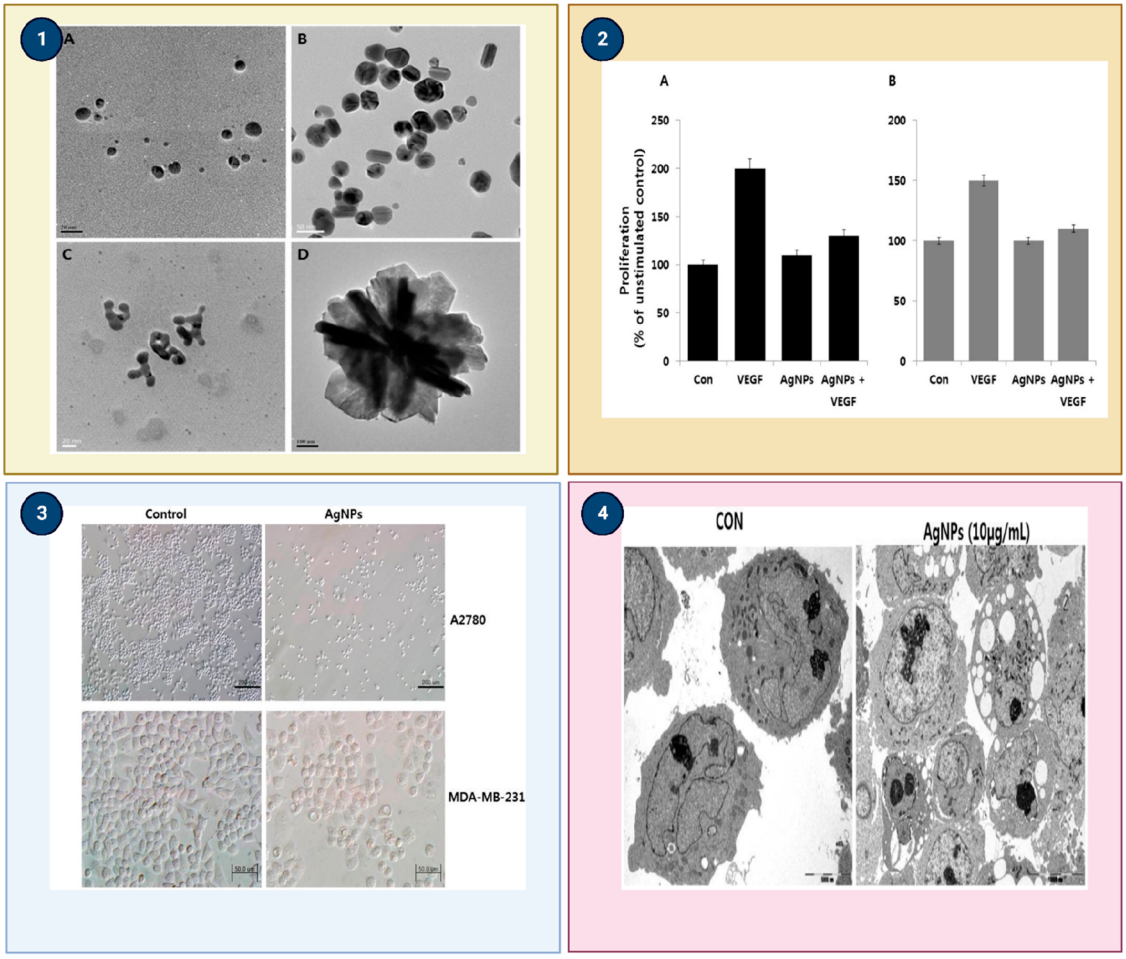

Figure 4. 1. Different shapes of AgNPs produced from various Bacillus species. (A) Spherical shape, (B) mixed shaped, (C) heavily branched, (D) flower-shaped AgNPs. 2. Various characterization techniques employed for AgNPs. (A) X-ray diffraction spectra. (B) Fourier transform infrared spectra. (C) Determination of size by dynamic light scattering. (D) SEM image. (E) TEM image. 3. Graph illustrating the effect of AgNPs on VEGF induced. (A) Describes bovine retinal endothelial cells (BRECs) and (B) MDA-MB 231. The assay was performed after the exposure to AgNPs for 24 h. 4. Induction of accumulation of autophagolysosomals due to AgNPs in a human ovarian cancer cell. All the images are adopted under CCBY4 from ref 74. Copyright (2016) MDPI.

lamellar vesicles (LUVs), and small unilamellar vesicles (SUVs) with sizes ranging from 0.5 to 100 nm. SLNs are a new colloidal drug delivery system composed of physiological lipids that remain solid at both room and body temperature, with particles ranging in size from 50 to 1000 nm. Solid lipids, including mono-, di-, or triglycerides, fatty acids, and complex glyceride mixtures, form a matrix material for drug encapsulation, stabilized by surfactants or polymers. SLNs provide significant advantages, including site-specific targeting, long-term physical stability, controlled release of both lipophilic and hydrophilic drugs, labile drug protection, low cost, ease of preparation, and low toxicity effects on human granulocytes.[47] However, SLNs have some disadvantages, such as moderate drug-loading capacity and drug expulsion due to crystallization under storage conditions.[48] NLCs, a second generation of lipid-based nanocarriers, are a combination of solid and liquid lipids, developed to overcome SLN limitations. They have higher drug loading capacity and avoid drug expulsion during storage by preventing lipid crystallization. NLCs are composed of glyceryl tricaprylate, ethyl oleate, isopropyl myristate, and glyceryl dioleate, have particle sizes similar to SLNs, can be surface-modified and targeted, and offer controlled drug release. However, they also have disadvantages such as drug expulsion after polymorphic transition and low loading capacity.[49]

Metallic Nanoparticles. MNPs feature an inorganic metal or metal oxide center typically encased in an organic or inorganic substance or metal oxide shell.[62] Gold nanoparticles (AuNPs) (Figure 3), silver nanoparticles (AgNPs), and Fe_2O_3NPs have been used as contrast agents in imaging techniques and as carriers for drug delivery.[63] The biocompatibility, stability, and high absorption and scattering of light of AuNPs, the antimicrobial properties of AgNPs, and the magnetic moment of Fe_2O_3NPs have made them ideal for nanotheranostics.[7] Further research is needed to optimize their use in nanodiagnostics and nanotherapy.

AuNPs have been widely studied for their use in nanotheranostics due to their biocompatibility, stability, and high absorption and scattering of light.[65] AuNPs have been the focus of significant research in nanotheranostics to treat solid tumors.[66] AuNPs possess exceptional physical and chemical traits due to their varying shapes and dimensions. The core of AuNPs, made of gold, is primarily inert and nonharmful to living things. Additionally, producing AuNPs is a straightforward process, and the particles' size can be controlled within a specific range, typically between 1 and 150 nm.[67] Finally,

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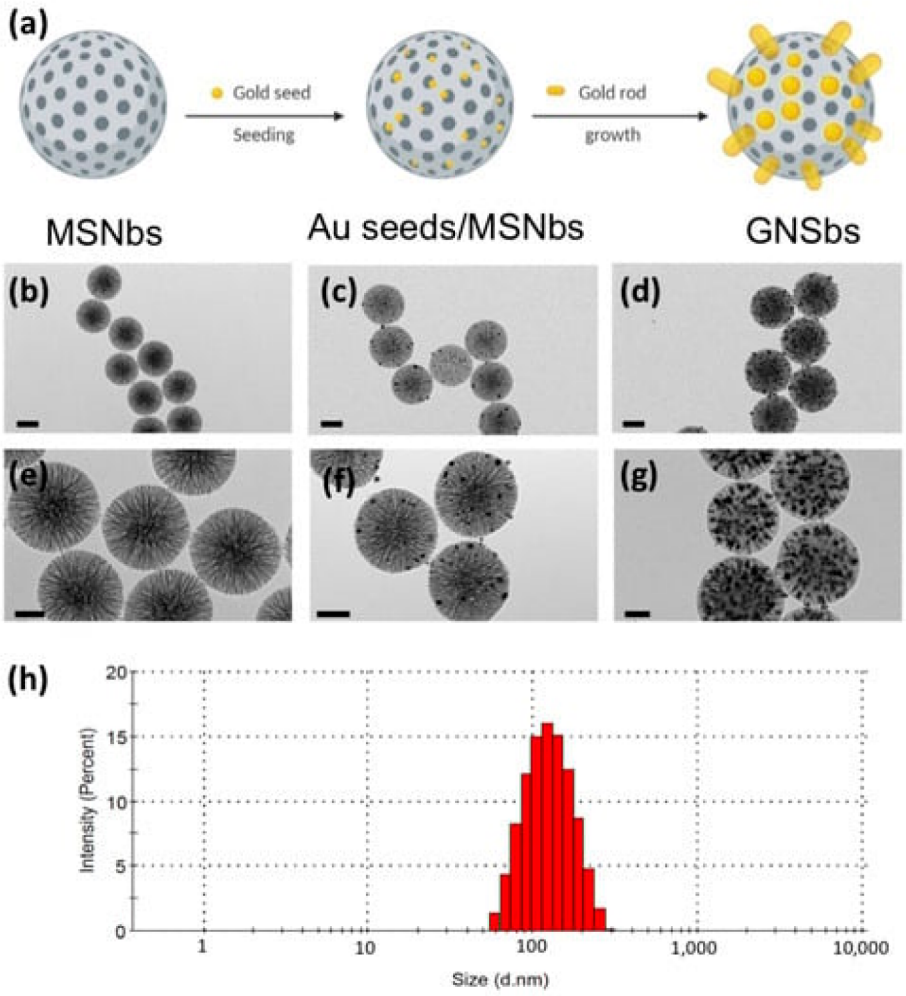

Figure 5. (a–h) Gold nanosesame beads (GNSbs). (a) Basic morphology of GNSbs. (b),(e) Images obtained from TEM of mesoporous silica nanobeads. (d) TEM of GNSbs. (c, f) TEM of gold-seed-filled porous silica nanobeads. (h) Describes the particle size distribution of GNSbs. (e, f, g) AuNPs in scale of 50 nm and (b, c, d) in the scale of 100 nm. Adopted under CCBY4 from ref 87. Copyright (2021), MDPI.

AuNPs can serve as efficient drug delivery systems as their various features and sizes allow for drug-controlled release in specific areas.[68] AuNPs are potential drug delivery agents due to their unique physical and chemical properties.[69] They can increase the pharmacokinetics of drugs, reducing side effects and allowing for targeted delivery of higher doses. AuNPs have been used to deliver small molecules and large biomolecules such as proteins, DNA, and RNA. However, the size, charge, and surface chemistry of AuNPs must be considered to create an effective delivery system.[14] Research has shown that AuNPs can be highly targeted in cancer cells and that the size of the AuNPs affects their uptake and intracellular fate.[70] Studies have also shown that AuNPs linked with drugs can be rapidly and efficiently concentrated in tumor cells. AuNPs can also cause specific photothermal damage to tumor cells when combined with near-infrared rays.

AgNPs also have antimicrobial properties and have been used in wound healing and treating infections.[71] AgNPs have been used as contrast agents in imaging techniques such as CT and photoacoustic imaging and as carriers for drug delivery.[72] Fe_2O_3NPs have a high magnetic moment and have been used as contrast agents in MRI. Fe_2O_3NPs have also been used for magnetic hyperthermia. The magnetic properties of Fe_2O_3NPs are utilized to generate heat when subjected to an alternating magnetic field, leading to the destruction of cancer cells.[73] Refer to Figure 4 for a discussion of AgNPs as a potential anticancer agent.

MNPs have several general properties that make them advantageous for theranostics, such as nanometric size, improved permeability retention, high surface area for molecular therapeutic binding, and surface functionalization with cancer-homing ligands for cancer treatments.[75] Moreover, due to their inherent biocompatibility, affordability, and unique magnetic properties under external magnetic fields,[76] MNPs represent a significant category of NPs in the current theranostic research.[77] The magnetic characteristics of MNPs typically include ferromagnetism and superparamagnetism.[78,79] Theranostics is currently receiving a lot of interest from MNPs such as gadolinium, nickel, manganese, and iron oxide-based nanoformulations.[80,81] Most nanoformulations used in theranostic applications are neutralized because charged NPs can connect to cells in an unintended manner, while neutral MNPs can lengthen blood vessel circulation times.[79] MRI positron emission tomography and single-photon emission computed tomography frequently use surface-functionalized MNPs as contrast agents.[82,83] MNPs are also often employed to generate heat at the targeted cells. A well-researched method for tumor-targeted drug delivery is magnetoreception or gene transfection

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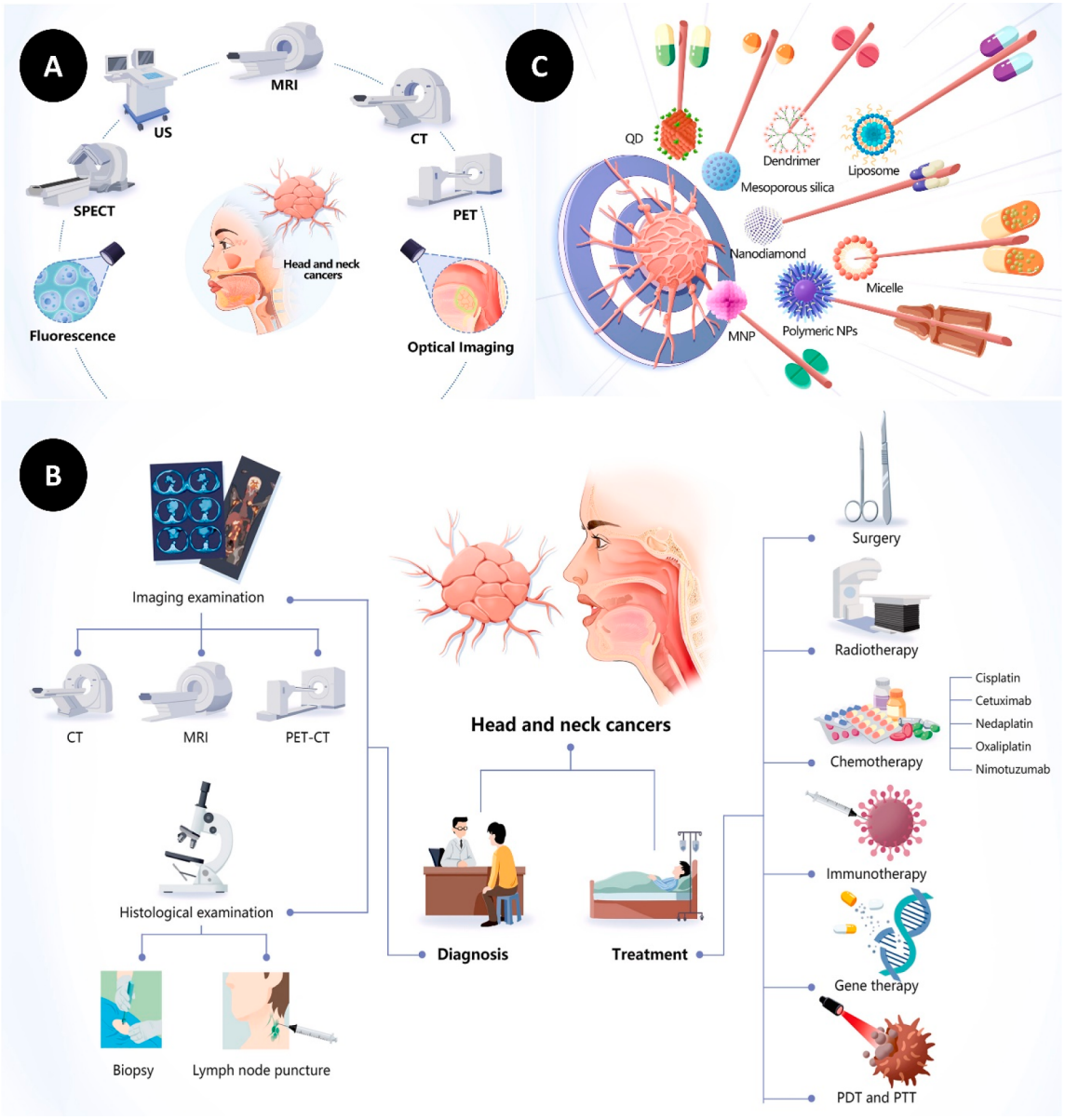

Figure 6. Management of head and neck cancer. (A) Imaging detection of head and neck cancers. (B) The diagnosis of HNC often utilizes clinical manifestations: imaging examinations such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)-CT, and histological examinations such as biopsy and lymph node puncture. The main treatments for early HNC include surgery, radiotherapy, chemotherapy, immunotherapy, gene therapy, photodynamic therapy (PDT), and photothermal therapy (PTT). (C) The main components of NM-based drug delivery systems include a nanocarrier, targeting moiety (e.g., aptamers, receptor-specific peptides, or monoclonal antibodies), and cargo (the desired chemotherapeutic drugs). Adopted under CCBY4.0 from ref 107. Copyright (2023) Elsevier B.V.

utilizing MNPs. Magnetofection can be used effectively in target drug delivery.

Gold−Silica Hybrids. Uncoated gold nanorods may aggregate in solutions and melt when exposed to laser light, both of which significantly alter their optical characteristics.[84] However, they can withstand aggregation and shape change under a variety of circumstances when their surface is suitably treated or chemically modified using silica, thereby preserving their optical characteristics.[85] Studies by Mitichei et al. showed that a tightly bound silica shell surrounding gold nanorods effectively prevents the production of a hydroxyl radical and singlet oxygen. Furthermore, numerical simulations that account for the application of short pulses of laser light demonstrate that the plasmonic field improvement at the nanoparticle area is reduced after the silica layer is added, rendering them ideal for a variety of biological advancements[86] (refer to Figure 5).

Also, studies conducted by Mueller et al. demonstrated hydrophobically modified, silica-coated gold nanorods as a versatile theranostic agent. The studies also showed that when contrasted with passive drug release in the absence of ultrasound, ultrasound-mediated circumstances resulted in a 2-fold higher release of nanomedicines.[88] He et al. reported a high-performance combination treatment for ablating cancer cells that combined photothermal therapy with chemotherapy to increase therapeutic effectiveness using silica-encapsulated gold nanorods.[89] Numerous photoresponsive applications are possible using gold nanorods, such as photothermal therapy, chemotherapy, imaging, and cancer treatment.

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Gold Nanoparticles. Since all the catalytic, magnetic, and optical properties of gold nanoparticles are influenced by their size and shape, a lot of attention has recently been paid to controlling the shape and size of gold nanoparticles. Also, due to their compatibility, conjugation with biomolecules, and adjustable optical characteristics that are caused by the shape and size of the gold nanoparticles, they play a significant role in biological sciences.[90] Additionally, gold nanoparticles display a variety of shapes, including spherical, suboctahedral, decahedral, icosahedral multiple-twined, tetrahedral, nanotriangles, hexagonal (platelets), and nanorods. In contrast to spherical nanoparticles, triangular gold nanoparticles exhibit desirable optical characteristics.[91]

Metallic nanoparticles have intrigued scientists for more than a century, and they are now widely used in engineering and the biological sciences.[92,93] The remarkable antibacterial characteristics of silver nanoparticles against harmful viruses, bacteria, and other nucleus-containing pathogens have been shown to make them particularly helpful.[94] The scientific community also believes that these metallic nanoparticles are harmless when used for gene and medication delivery. Additionally, metallic nanoparticles can simultaneously provide therapeutic and diagnostic options.[95]

Quantum Dots. Quantum dots (QDs) are nanoscale semiconductor particles with unique optical and electronic properties. They have gained attention recently due to their potential applications in various fields, including nanomedicine.[96] In particular, QDs have shown promise as a platform for nanotheranostics in solid tumors. QDs have been utilized as nanotheranostics due to their unique properties, such as high photostability, large absorption cross-section, and size-tunable fluorescence emission. This makes them suitable for imaging and therapeutic purposes.[97,98] To date, various types of QDs from groups II−VI such as Zn(S, Se), Cd(S, Se, Te), IV−VI Pb(S, Se), I−VI Ag_2(S, Se), II−V Cd_3(P, As)$_2$, and III−V In(P, As) as well as ternary I−III−VI QDs (where I = Cu or Ag, III = Ga or In, VI = S or Se) have been successfully utilized in biomedical fields.[99,100] QDs comprise a fluorescent core surrounded by a crystal shell that protects the center from ionization within biological systems.[98] Their exceptional optical properties make them ideal for biomedical applications. Their narrow and symmetrical emission profiles provide color purity and accurate emission stability. Their broad excitation range and high molar absorption coefficients allow for high-throughput detection. Moreover, their high photoluminescence (PL), quantum yield (QY), and resistance to photobleaching offer the potential for long-term monitoring of biological processes. Additionally, their relatively long PL lifetimes enable the reduction of autofluorescence.[101] As a result, QDs have been proposed as versatile contrast imaging agents that can be applied to a range of imaging modalities, including infrared fluorescence, positron emission tomography, CT, MRI, and PA imaging.[81,101] QDs can be engineered with various biological molecules, such as antibodies, peptides, and aptamers, which improve their biocompatibility for targeted drug delivery.[102]

Wang et al.[103] showed that graphene QDs conjugated with folic acid (FA) could be used for antitumor drug delivery. Their biocompatibility, optical properties, high surface-to-volume ratio, and carboxylic groups for conjugation with anchoring molecules make them suitable for targeted drug delivery and real-time monitoring. QDs can also be used as carriers for siRNA (short, double-stranded, small interfering RNAs) to induce RNA interference and inhibit protein translation. They can be photostable beacons for monitoring siRNA delivery.[104] QDs' therapeutic efficacy has led to their application in photothermal (PTT) and photodynamic (PDT) therapy.[74] PTT requires NIR-absorbing platforms that induce hyperthermia at the target site and cause cellular damage, while PDT requires photosensitizers to generate reactive oxygen species (ROS) to destroy cancer tissues. However, these applications may have limitations with other NPs and require further study. QDs such as $Cu_2(OH)PO_4$ have been identified as promising agents to overcome these limitations and enhance disease treatment.[105] Tungsten sulfide QDs have also shown promise for synergistic PTT and radiotherapy with dual-modal imaging. Carbon QDs develop into an intelligent theranostic nanomaterial for detecting and treating cancer. Yang-Wang et al. synthesized a biofriendly trichrome-tryptophan-sorbitol carbon QD from natural tryptophan via the one-pot hydrothermal method that shows stronger green fluorescence in hepatocellular carcinoma (HCC), generates reactive oxygen species leading to autophagy of HCC cells, and performs significant tumor inhibition by inducing autophagy through a p53-AMPK pathway *in vitro* and *in vivo* with minimal systemic toxicity.[106] However, toxicological effects of QDs, especially those based on heavy metals, have been reported, so further study is needed before clinical application. Refer to Figure 6 for an understanding of the application of various techniques in the management of head and neck cancer.

Aptamers are single-stranded RNA or DNA molecules that can bind specifically to target molecules, such as proteins or small molecules, through their specific 3D structures.[108] They have been used in nanotheranostics, which can act as molecular targeting agents for delivering diagnostic and therapeutic agents to specific cells or tissues.[109] Aptamers can be conjugated to NPs, such as QDs or liposomes, and direct them to specific cellular targets. This can enhance the specificity and efficiency of disease diagnosis and treatment. Moreover, aptamers can also be used as therapeutic agents themselves through their ability to modulate the activity of target molecules or to trigger specific cellular responses.[110,111] Using aptamers in nanotheranostics holds great promise for developing new and effective treatments for various diseases.

Carbon Quantum Dots. Carbon-based quantum dots, otherwise known as carbon dots (CDs) or C-dots, were first discovered in 2004 from the purification of single-walled carbon nanotubes and have been since made using laser ablation and hydrothermal methods. CDs are quasi-0D multicolor photoluminescent carbon nanomaterials possessing high quantum yield, good biocompatibility, excellent stability, strong absorption, and small sizes. These intrinsic properties of carbon dots are attractive candidates for important applications such as nanomedicine, catalysis, energy storage, and optoelectronics.[112] By combining ^{13}C labeling and whole-body imaging, Yang et al. were the first to examine the biodistribution pattern of carbon dots in 2009. The mice's C-dot biodistribution and translocation were completed. It was discovered that carbon dots can easily spread throughout the entire body but are unable to penetrate the blood−brain barrier (BBB). Moderate buildup was seen in some organs, including the spleen, liver, and kidney.[113] Additionally, by labeling the carbon dots with ^{125}I, Tao et al.[114] carried out a toxicity and biodistribution investigation. A two-compartment model was used to conduct a pharmacokinetic investigation of carbon dots. C-dots had a 0.1 h distribution half-life and a 2.1 h clearance half-life. With

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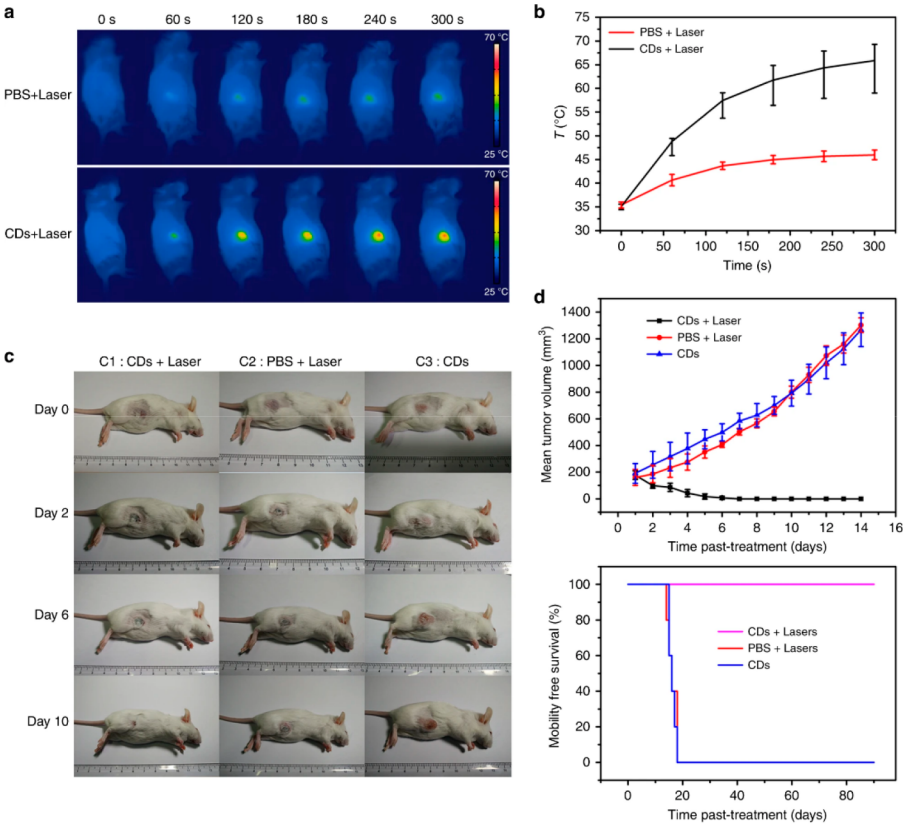

Figure 7. (a–d) Photothermal therapy of CDs following intravenous delivery. (a) IR thermal images of mice with CDs injected and irradiated at 10, 60, 120, 180, 240, and 300 s at the tumor region by a 655 nm laser. (b) Mouse tumor temperature as a function of irradiation duration. (c) Photographs of tumor growth. (d) Tumor growth curves following treatment. Adapted under CCBY4 from ref 120. Copyright (2018) Light: Science & Applications license.

the exception of the brain, there was a moderate buildup of carbon dots in the spleen, liver, and kidney, which was consistent with Yang et al.

Sun et al. conducted *in vitro* and *in vivo* studies on carbon dots, examining their impact on MCF-7 cells (human breast cells) and HT-29 cells (human colorectal adenocarcinoma). They employed Trypan Blue and MTT assays to evaluate viability, proliferation, and cell mortality after exposing the cells to carbon dots. The carbon dots were synthesized using PEG1500N laser ablation and surface passivation techniques. Results demonstrated that these nanoscale carbon particles exhibited robust photoluminescence in solution and the solid state, even with simple surface passivation. The emitted light from the carbon dots remained stable without blinking or photobleaching. The researchers concluded that these highly emissive carbon dots could have applications comparable to or surpassing those of extensively studied silicon counterparts.[115]

In theranostic applications, NIR carbon dots have been used to photothermally image and ablate H22 tumors generated from the subcutaneous injection of H22 hepatoma ascites.[116] Internalized CDs in the tumors were irradiated with a 655 nm laser, raising internal temperatures to over 65 °C and causing significant tumor volume reduction following treatment (Figure 7). To increase tumor uptake, carbon dots have been synthesized to mimic amino acids to facilitate the specific uptake of nanoparticles into tumors and cancer cells via specific carrier transporters such as LAT1. Here, carbon dots enabled the imaging and delivery of therapeutics to brain tumors with high specificity and efficiency in a U87-tumor-bearing mouse. Theranostic carbon dots have also been engineered to produce NIR-II emission for deep *in vivo* imaging and photothermal therapy. These carbon dots are a new type of NIR-II CD-based probe synthesized from watermelon juice as the carbon source and are small enough to be physiologically cleared renally.[117] Aside from photothermal treatments, carbon dots may also be conjugated with folic acid and combined with chloroquine or docetaxel to deliver therapeutics.[118] CDs have also been functionalized with dendrimers and complexed to plasmid DNA to deliver genetic material.[119] In summary, CDs are an exceptional alternative to conventional bioimaging probes such as quantum dots, which suffer from toxicity issues. Their outstanding optical properties combined with their excellent biocompatibility and simple, low-cost synthesis make carbon dots suitable candidates as next-generation bioimaging fluorescent probes.

NANOPARTICLE STRATEGIES IN THERANOSTICS

The development of nanosensor and nanomedicine technologies in recent years has paved the way for promising ways to use nanotheranostics in cancer treatment. The transport and effectiveness of biological and conventional treatments can be improved by conjugating nanotheranostics agents of various types, such as gold, silver, and magnetic NPs, along with nanoshells and nanocages. This nanotheranostics strategy is based on controlling NPs (1–200 nm) by taking advantage of certain unique qualities, including large surface area, optical and magnetic characteristics, low melting point, and mechanical strength.[121] They are now frequently utilized for targeted

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drug administration, aptamer delivery, and diagnostic imaging of various disease stages by MRI, CT, PET, single photon emission tomography, photoacoustic imaging and surface-enhanced Raman spectroscopy (SERS), ultrasound, etc.[121] Because of their potential as therapeutic and diagnostic tools, protein-based NPs have recently attracted much attention.[122] DNA origami, a synthetic form of 3D DNA lattices, has also been employed as a theranostic agent, allowing different chemotherapeutic drugs to be segregated into the hollow areas inside the lattice. This tactic has been proposed to improve the effectiveness of controlled drug delivery and cancer biomarker identification.[123] Different thrombolytic agents can be delivered through microbubbles of perfluorocarbon NPs and echogenic liposomes, along with superparamagnetic iron oxide NPs or poly(acrylic acid)-coated magnetic NPs.[124]

By targeting proteins unique to a particular cancer tissue type, nanotheranostics drugs can be employed as a tailored cancer treatment strategy. This is made possible by a targeted anticancer drug delivery strategy that allows for real-time tracking of the biodistribution and drug release of NPs used to inhibit solid tumors, such as magnetic, gold, silica NPs, and nanocarbon organic NPs, as well as liposomes, micelles, dendrimers, proteins, and biopolymers.[125−128] Numerous biomedical applications have been made possible by nano-theranostics, including effective drug administration across the blood−brain barrier, multimodal and combinatorial therapy, siRNAs, and a combination of bioligands for specific molecular targeting.[17] NPs can successfully transfer a range of targeted agents (such as peptides, aptamers, monoclonal antibodies, nucleic acids, chemotherapeutics, etc.) to malignant cells because of their surface alterations.[129,130] Diverse NPs can be utilized simultaneously to visualize tumor development using MRI, fluorescence, or other optical techniques. So, using a nanotheranostics technique, the prognosis of various cancer types can be identified and tracked, along with targeted and site-specific tumor cell obliteration. In this section, we outline nanoparticle design strategies associated with imaging and the therapeutic treatment of solid tumors. We review imaging modalities such as MRI, fluorescence, and PET; therapeutic strategies such as drug nanoencapsulation and photodynamic therapy; and targeting strategies such as employing biomimetic materials to increase tumor uptake efficiency.

MAGNETOTHERANOSTICS

MNPs have attracted much attention from cancer nano-theranostics in recent years due to their numerous applications in MRI and multimodal imaging, efficient delivery of both gene and conventional chemotherapies, and the hyperthermal killing of cancer cells.[131] MNPs are smaller (∼100 nm) than traditional theranostic agents, allowing quicker delivery and increased tissue penetration.[132] MNPs, particularly iron oxide NPs, have high surface area-to-volume ratios that allow for a wide range of pre- and postsynthesis modifications, including chemotherapeutic drugs and targeting moieties.[133] To detect cancer cells in soft tissue, modified MNPs can be utilized as contrast agents in MRI scans. Unlike MNPs that have not been modified, modifications can also be made to lessen their cytotoxicity.[134] To improve their activity, surface changes with 3-(2-aminoethyl amino) propyl trimethoxysilane and further conjugation with polyethylenimine-FA are surface treatments with MNPs. These treatments enhance the specificity of cancer cells for efficient therapy.[134] Targeted drug delivery, slowing the growth of tumors, and employing MRI contrast imaging to track MNP accumulation in tumor tissue are the main ways that MNPs are utilized to treat glioblastoma.[135]

Sahu et al. employed a PEGylated Tb^{3+} coating on IONPs combined with Ce^{3+}-sensitized gadolinium phosphate nanorice to increase the multifunctionality of IONPs.[136] This multi-functional nanorice became a successful drug delivery system for DOX due to its mesoporous structure and abundance of negatively charged functional groups on the surface. Using a confocal laser scanning microscope, the nanorice produces a green light that enables tracking and monitoring its cellular uptake and accumulation. Using the MCF-7 and HeLa cell lines, the impact of these modified IONPs loaded with DOX was examined *in vitro*. The DOX-loaded IONPs appear to hold promise for future improvements in the treatment efficacy of these malignancies.[136]

For effective drug delivery, therapy shown in 4T1 tumor-bearing female balb/c mice, and trimodal image-guided monitoring in the presence of NIR/X-ray, preadsorbed IONPs on PEGylated WS2 nanosheets coated with DOX-loaded mesoporous silica (WS2-IO@MS-PEG) can be used.[137] In addition, PTT is a noninvasive therapeutic strategy with many advantages, including increased selectivity, decreased systemic toxicity, and remote controllability.[138] Yu et al. developed MoS_2/Fe_3O_4 nanotheranostics for magnetically targeted photothermal therapy guided by magnetic resonance/photoacoustic imaging MoS_2 that transformed NIR light into heat, and Fe_3O_4NPs served as the target moiety that was directed by an external magnetic field to the tumor site.[139] The MoS_2/Fe_3O_4 composite (MSIOs) functionalized with biocompatible PEG was created using a straightforward two-step hydrothermal process. Additionally, the obtained MSIOs show good biofluid stability and minimal toxicity *in vitro* and *in vivo*. Due to their superparamagnetic characteristic and complete NIR absorption, the MSIOs can be used as a dual-modal probe for T2-weighted MR and photoacoustic tomography imaging. In addition, we show that magnetically focused photothermal ablation of cancer is successful. In addition, this showed that magnetically focused photothermal ablation of cancer is successful. These findings point to the potential of the multifunctional MSIOs for cancer theranostics and demonstrate the potential for localized photothermal ablation of cancer that is spatially driven by the magnetic field.

MoS_2−iron oxide (MoS_2−IO) nanocomposites can be further modified and used as a PET theranostic agent by surface absorbtion of the positron-emitting radioisotope ^{64}Cu. This configuration enables the imaging of tumor growth and metastasis by producing a potent *in vivo* system capable of photothermal ablation (MoS_2), magnetically guided delivery (IONPs), and 3D imaging of the body/physiological processes (^{64}Cu). In PTT, MoS_2−IO-(d)PEG, which are MoS_2−IO nanocomposites modified with double PEGylation, have demonstrated potential for tumor ablation in 4T1 (murine breast cancer) cells. When mice tumors were injected with MoS_2−IO-(d)PEG and subjected to NIR laser, the surface temperature increased by roughly 51 °C in 5 min; however, when MoS_2−IO-(d) PEG was not present, the temperature increased by only 5 °C.[139]

By incorporating MRI contrast agents into polymeric nanoparticles, it becomes possible to enhance the visibility of tumors in MRI scans. These contrast agents can be encapsulated within or attached to the surface of polymeric nanoparticles. One example of a copolymer used for this purpose is PLA-TPGS (poly(lactic acid)-D-α-tocopheryl poly-

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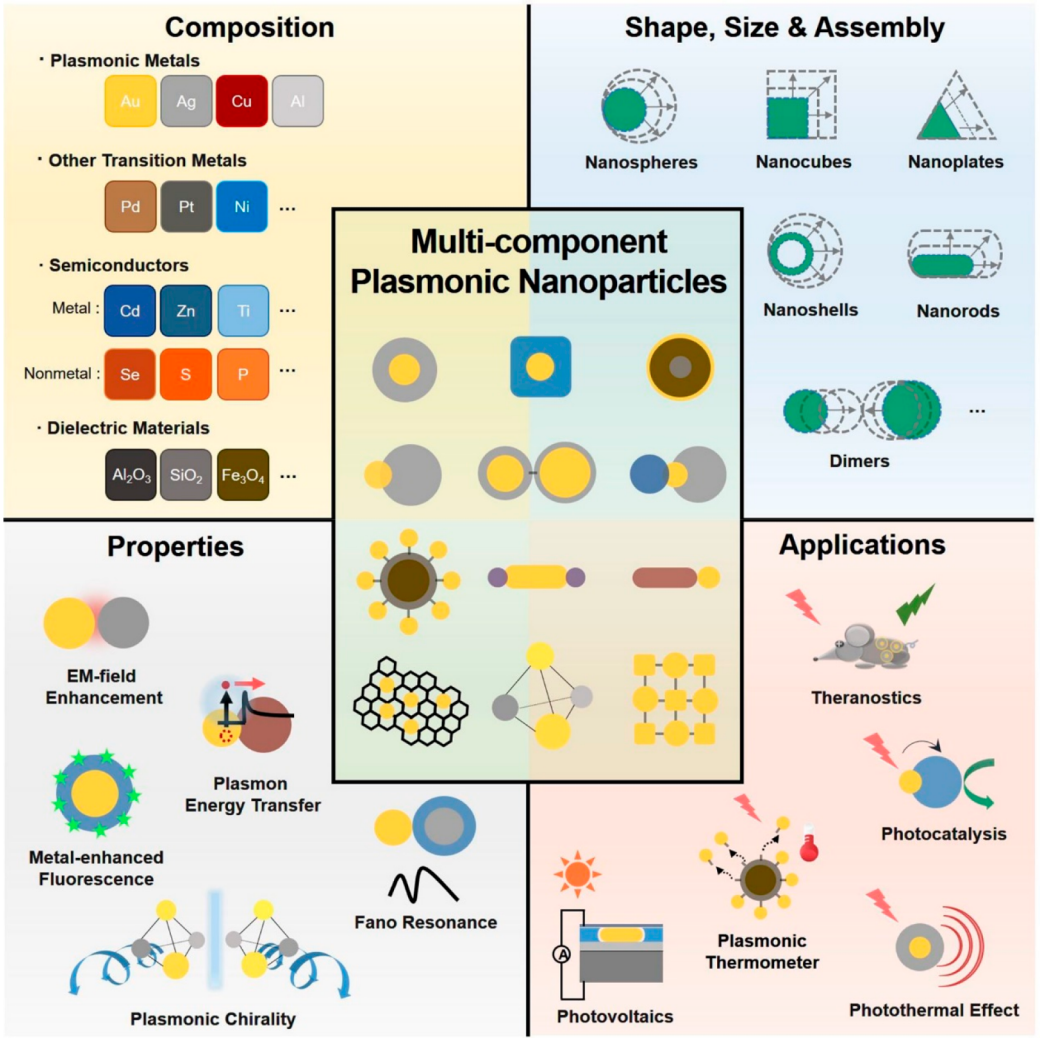

Figure 8. Plasmonic nanoparticle. It consists of plasmonic metals, semiconductors (metal and nonmetal), dielectric material, and other transition metals. It is available in various shapes such as nanospheres, nanocubes, nanoplates, nanoshells, nanorods, and dimers. It is enriched with various properties such as EM-field enhancement, plasmon energy transfer, meal-enhanced fluorescence, Fano resonance, plasmonic chirality, etc. It is vividly used in theranostic approaches, various photocatalyses, plasmonic thermometers, photothermal, and many more fields. Adopted under permission from ref 146. Copyright (2019) American Chemical Society.

ethylene glycol 1000 succinate). It becomes a multimodal imaging approach by combining PLA-TPGS with MRI contrast agents and fluorescent contrast agents. The addition of fluorescent contrast agents allows for visualization using fluorescence imaging techniques in addition to MRI. Furthermore, a specific contrast dye called Cy5.5 can be conjugated with iron nanoparticles, creating a complex that combines the fluorescent properties of Cy5.5 with the MRI contrast capabilities of iron nanoparticles. The resulting complex enables tumor imaging using both MRI and fluorescence techniques.[140] In addition, dendrimers serve as another type of delivery agent characterized by their highly branched spherical structure. A research study demonstrated a specific dendrimer as a theranostic delivery system capable of carrying both an MRI contrast diagnostic agent called Cy5.5 and the anticancer drug paclitaxel. This dendrimer exhibited high cellular uptake; i.e., it was effectively taken up by the target cells. Moreover, it displayed reduced adverse effects on nontarget organs, minimizing potential harm to healthy tissues due to the dendrimer's design and properties.[141]

PLASMONIC THERANOSTICS

NPs made of silver and gold have enormous potential as theranostic agents. They have the benefits of simplicity in synthesis, bioconjugation, and surface changes that make AuNPs more biocompatible and less cytotoxic.[142] With the same multimodal imaging capabilities and application flexibility as MNPs, AuNPs provide a greater range of therapeutic and diagnostic utility for treating cancer.[132] SERS nanoantennas can be conjugated with the FDA-approved antibody cetuximab, inhibiting cancer via epidermal growth factor receptor deactivation.[143,144] SERS nanoantennas are created by capping AuNPs with a Raman reporter entrapped in larger polymers. Raman signals generated by the SERS nanoantenna can be recorded simultaneously to measure a tumor's size and inhibition.[144] SERS nanoantennas are an up-and-coming nanotheranostics agent for treating ovarian cancer and neuroblastoma due to their greater payloads than lipofection, effective cellular absorption, low toxicity, quick endosomal escape, and increased half-lives[145] (refer to Figure 8).

Gold nanoclusters (AuNCs) are yet another exciting class of theranostic agents due to their characteristics including

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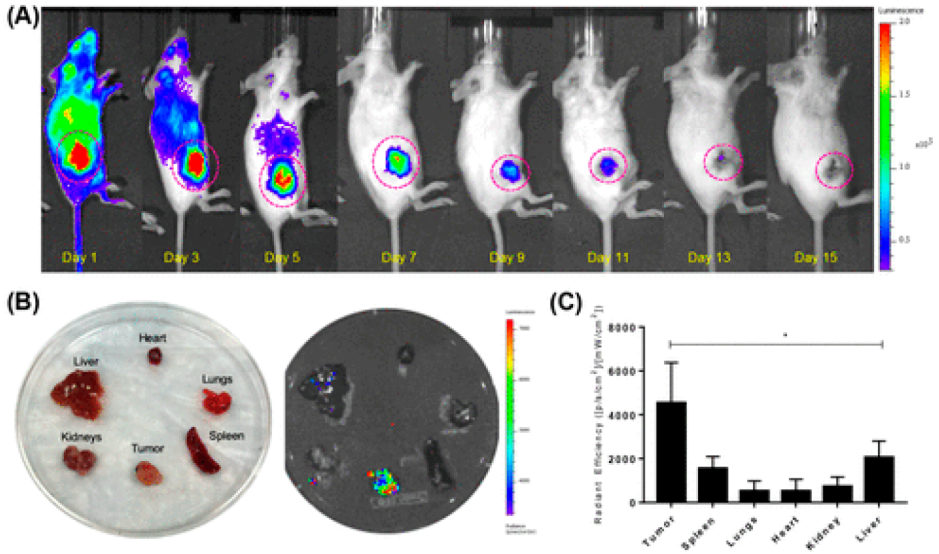

Figure 9. Monitoring of ^{90}Y-DOTA-UPSN in a tumor model using Cerenkov luminescence imaging. (A) Mice injected with 90Y-DOTA-UPSN exhibit tumor accumulation. (B) Relative UPSN accumulation in organs less than tumor uptake. (C) Quantified radiant intensity of UPSN uptake in organs vs tumor. Reprinted (adapted) with permission from ref 156. Copyright (2021) American Chemical Society.

minimal photobleaching, little cytotoxicity, and improved Stokes-shifted emission.[147] Red, green, and blue fluorescences that can be used for imaging are released by fluorescent AuNCs coupled with chitosan biopolymers, and these fluorescences are identified by taking UV−vis spectra. The therapeutic substances can be delivered to the target tissue via these NPs. For instance, using the prodrug 5-fluorocytosine (5-FC), which is transformed into the pro-apoptotic toxin 5-fluorouracil (5-FU) by the activity of the cytosine deaminase-uracil phosphoribosyltransferase (CD-UPRT) enzyme, AuNCs loaded with the suicide gene CD-UPRT can kill HeLa cells.[147]

A gold−silver nanoshell (Ag/AuNS) can be modified with glucose oxidase to selectively target, screen for, and destroy cancer cells in early stage malignancies.[148] Additionally demonstrated to be effective site-specific theranostic agents were gold-core gold-shell (Au@Au) or gold-core silver-shell (Au@Ag) NPs coupled with activatable aptamer probes (AAPs; carrying a fluorophore). As shown in A549 cells, such Au@Ag/Au-AAP nanoassemblies can be used for PTT guided by high-contrast imaging systems.[149] As anticancer theranostic drugs, biosynthesized (bAgNPs) are also helpful. For example, Olax scandens leaf extract and $AgNO_3$ combine to create b-AgNPs, which fluoresce brilliant red inside cells and could potentially be used as an imaging diagnostic tool. Significant anticancer activities in human breast cancer, murine melanoma, and lung cancer have been shown by these NPs.[150]

Natarajan et al. developed a unique cancer-targeting assembly comprising AuNPs with quantum dots, miR-491, and mAb-ChL6 connected through streptavidin/biotin to effectively transfect cancer cells and cause death in specific cancer cells for imaging and targeted therapy.[151] This study evaluated the capacity to target and induce apoptosis using confocal and electron microscopy. The study findings showed that miR-491 specifically caused apoptosis in breast cancer cells compared to healthy breast cells. Over 72 h, miR-491's ability to induce apoptosis was increased. Compared to untreated breast cancer cells, AuNP-coupled miR-491 displayed higher apoptotic effect (>80%) and transfection efficiency. An inductively coupled plasma mass spectrometer was used to estimate the microRNA transfected into the cancer cells. The imaging and treatment of breast cancer could benefit from this unique nanogene molecular assembly. The mAb-GNP-miR491-Qdot construct successfully transfected into the HBT3477 cells and caused apoptosis. This research work may also influence the development of clinical therapies for prevalent cancer forms.[151]

In another study, Zhu et al. developed multifunctional dendrimer-entrapped gold nanoparticles (Au DENPs) covalently coupled with alpha-tocopheryl succinate (α-TOS) for use in the theranostic treatment of certain cancers.[152] In this study, amine-terminated poly(amidoamine) dendrimers of generation 5 (G5.NH_2) were conjugated with fluorescein isothiocyanate, PEG-modified α-TOS, and PEGylated FA and used as templates to create Au DENPs. The remaining dendrimer terminal amines were then acetylated. Different methods were used to characterize the developed multifunctional Au DENPs. The authors demonstrated the water dispersibility and stability of the Au DENPs, which have a Au core size of 3.3 nm and 9.8 α-TOS molecules per dendrimer and are stable at various pH and temperature levels as well as in different aqueous media. The FA modification on the Au DENPs allows excellent targeted CT imaging of the cancer cells *in vitro* and the xenografted tumor model *in vivo*. It also provides for efficiently targeting the particles of cancer cells overexpressing FA receptors (FAR). The therapeutic activity is unaffected by α-TOS covalent conjugation and substantially increased water solubility. Notably, the produced multifunctional Au DENPs can impart the precise therapeutic efficacy of α-TOS to the FAR-overexpressing cancer cells *in vitro* and the xenografted tumor model *in vivo* due to the function of FA-directed targeting. The created multifunctional Au DENPs have the potential to be innovative theranostic nanoplatforms for targeted CT imaging and cancer therapy.[152]

Gold nanoparticles have garnered significant attention in scientific research due to their extraordinary plasmonic characteristics and the advantageous ratio between their surface area and volume. These properties have prompted extensive exploration of their potential utility in detecting

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biomarkers. Biomarker molecules or substances in elevated amounts in the blood, serum, or specific cancerous regions play a crucial role in aiding diagnosis. However, detecting specific biomarkers in extremely low concentrations presents a formidable challenge, necessitating the development of highly sensitive detection strategies.[153] Photoacoustic imaging (PAI) is an imaging technique that offers noninvasive real-time information by converting absorbed short-pulsed laser energy into ultrasound signals through the thermoelastic effect. These ultrasound waves are captured by transducers placed on the tissue surface, which convert the mechanical waves into electrical signals. After appropriate processing, an image is formed, representing the distribution of absorbed optical energy. Unlike ultrasound imaging, PAI overcomes the limitations associated with the mechanical properties of biological tissues and provides enhanced tissue contrast based on the optical properties of different tissues. Gold nanoparticles (AuNPs) are particularly advantageous in PAI due to their high molar extinction coefficient, which enables maximum light absorption. They also offer optimal tissue penetration, minimizing interference from intrinsic chromophores, and are not susceptible to photobleaching. In PAI, AuNPs can serve as exogenous contrast agents for detecting various tumors by monitoring functionalized receptors' passive or active accumulation. They can also be utilized for intravascular PA imaging of macrophages in atherosclerotic plaques. Moreover, PAI using gold nanoparticles as contrast agents enables the tracking of stem cells. GNPs can be efficiently loaded into stem cells and are not significantly exocytosed. A contrast agent system composed of inert gold nanorods bound with a ROS-sensitive near-infrared dye (IR775c) allows for real-time tracking of cell viability with the high spatial and temporal resolution, facilitating the assessment of the efficacy and contribution of cell therapies.

HYBRID NANOTHERANOSTICS

Silica nanoparticles (SiNPs) have unique features that make them valuable as nanotheranostic agents, including biodegradability, biocompatibility, wide surface area and pore volume, and thermal and chemical stability (Figure 9). The main benefit of SiNPs as a theranostic platform comes from their porosity. By managing the porosity, various theranostic cargos can be delivered to multiple cancer cell types in a controlled, sequential, and multifunctional manner.[132] For instance, porous SiNPs coupled with Alexa Fluor-488, iRGD peptide, and dibenzocyclooctyl can be utilized as a theranostic agent.[154] As a nanotheranostic agent, docetaxel and silica nanorattles conjugated with luteinizing hormone-releasing hormone (LHRH), *Pseudomonas aeruginosa* exotoxin 40 (PE40), and docyanine green fusion protein can be employed (antimitotic chemotherapeutic). Following LHRH's targeting of cancer cells, docetaxel inhibits cell proliferation, and PE40 exhibits cytotoxic action. For image-guided drug delivery and therapy for cancer, the docyanine green signal is recorded.[155]

Europium- (Eu) and Gd-conjugated mesoporous SiNPs (MSN) have been evaluated as theranostic agents (EuGd-MSN). EuGd-MSN has been utilized in conjugation with camptothecin (CPT) (EuGd-MSN-CPT) to target cancer cells while concurrently assessing the effects of the application using MRI and fluorescence imaging.[157] Qianjun He et al. developed mesoporous carbon@silicon-silica nanotheranostics for synchronous delivery of insoluble drugs and luminescence imaging.[158] In this study, using a bottom-up self-assembly strategy in conjunction with an *in situ* one-step carbonization/crystallization method, a hierarchical theranostic nanostructure (CS-MSNs) was developed. This structure contains carbon and Si nanocrystals encapsulated in mesopores and within mesoporous SiNPs. In addition to having a large payload of insoluble medicines and a particular NIR-to-Vis luminescence imaging characteristic, CS-MSNs also showed a limited size distribution. The bioconjugated CS-MSNs with a PEGylated phospholipid compound and hyaluronic acid demonstrated excellent dispersivity. They could selectively target cancer cells overexpressing CD44, deliver insoluble drugs into these cells, subsequently kill them effectively, and fluorescently image them simultaneously in a novel and appealing NIR-to-Vis luminescence imaging fashion, offering a promising opportunity for cancer theranostics.[158]

GRAPHENE THERANOSTICS

A two-dimensional layer of sp^2-bonded carbon known as graphene is anticipated to offer ground-breaking uses in nanotechnology.[159] Nanomaterials based on graphene oxide (GO) have recently attracted much interest. Graphene-based nanotheranostics agents have several physical benefits over other nanotheranostics platforms, including a large surface area, colloidal stability, ease of surface modification and functionalization, and superior electrical and mechanical capabilities. Graphene-based nanotheranostics agents, such as graphene nanosheets, which have shown increased apoptosis in $CD44^+$ KB carcinoma cells utilizing NIR imaging, can allow image-guided tumor ablation via synergistic PTT.[160]

Yang et al. demonstrated that the poly(amidoamine) dendrimer-grafted gadolinium-functionalized nanographene oxide nanoparticles (Gd-NGOs) are efficient delivery systems for chemotherapeutic drugs as well as highly specialized gene-targeting compounds like miRNAs to cancer cells.[161] Epirubicin (EPI), an anticancer drug, could simultaneously bind to the positively charged Gd-NGO surface and interact with the negatively charged Let-7g miRNA. They discovered that this combination of Let-7g and EPI (Gd-NGO/Let-7g/EPI) established noticeably higher transfection efficiency than Gd-NGO/Let-7g or Gd-NGO/EPI but also produced more potent inhibition of cancer cell development. The authors used human glioblastoma (U87) cells as a model. When compared to Gd-NGO/EPI (3.4 mg/mL EPI), the concentration of Gd-NGO/Let-7g/EPI needed to inhibit cellular growth by 50% (IC_{50}) was much lower (to the equivalent of 1.3 mg/mL EPI). Additionally, Gd-NGO/Let-7g/EPI could be employed as a contrast agent for MRI to locate and quantify drug delivery to tumor regions and determine the extent of blood−brain barrier opening. These findings indicate a potential nonviral vector for chemoembolization therapy and molecular imaging diagnosis in upcoming clinical applications.[161]

Taratula et al. developed a nanotheranostics system with novel low-oxygen graphene nanosheets chemically altered with polypropyleneimine dendrimers loaded with phthalocyanine (Pc) as a photosensitizer.[162] Such a molecular structure prevents graphene nanosheets from dampening the Pc's fluorescence, enabling fluorescence imaging. The developed nanoplatform was coupled with poly(ethylene glycol) to increase biocompatibility and LHRH peptide to deliver drugs precisely to tumors (Figure 10). Notably, photothermal treatment using graphene nanosheets and Pc's ROS production utilized low-power NIR irradiation of a single wavelength. With a lethal effectiveness of 90%−95% at low Pc

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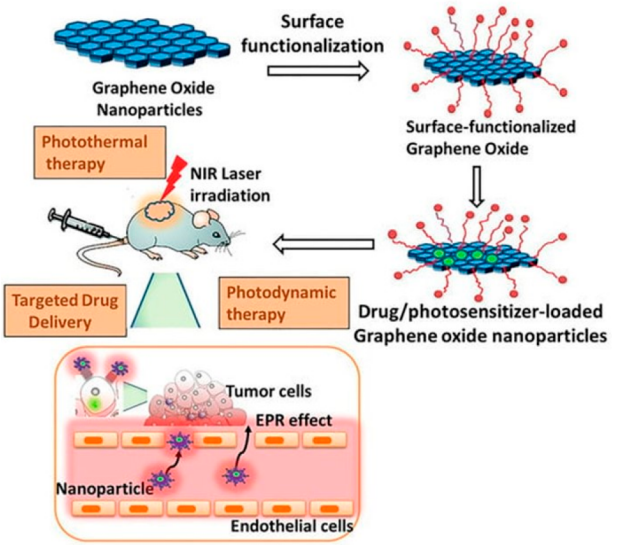

Figure 10. Graphene oxide nanoparticles, which on modification with the help of various agents on the surface lead to incorporation of targeted drug delivery, photodynamic drug delivery, and photothermal drug delivery. This targeted the tumor cells and helps in management of tumors. Adopted under CCBY4 from ref 163. Copyright (2020) MDPI.

and low-oxygen graphene doses, combinatorial phototherapy improved the demise of ovarian cancer cells, likely giving cytotoxicity to the combined effects of produced ROS and mild hyperthermia. Pc put onto the nanoplatform has been proven effective as a NIR fluorescent agent for imaging-guided drug delivery in an animal investigation. Because of this, the developed Pc−graphene nanoplatform has excellent potential to be a successful NIR theranostic probe for imaging and combined phototherapy.[162]

BIORESPONSIVE THERANOSTICS

Lipid- and polymer-based nanotheranostics agents provide the widest variety of cellular compatibilities, biodegradability, quick cellular absorption, and no toxicity. Due to their diagnostic applications, stimulation generation, thermodynamic stability, targeting ability, circulating longevity, and ease of *in vivo* customization,[164,165] lipids[166,167] and polymers[168−170] have been frequently used as nanocarriers. Due to their dual *in vivo* imaging modes, superparamagnetic MRI and fluorescence imaging in NIR, PEGylated liposomes linked with IONPs and infrared dye (L-IONP/DiR) are promising as theranostic agents.[171]

For targeted cancer therapy and imaging, Parhi et al. examined the imaging and diagnostic capabilities of Trastuzumab (Tmab)-functionalized lipid-based NPs loaded with rapamycin and QDs.[172] Various *in vitro* cellular experiments were used to evaluate the therapeutic evaluation of drug-loaded NPs. In HER 2 positive SKBR 3 breast cancer cell line experiments, the results demonstrated the improved therapeutic efficacy of targeted drug-loaded NPs over native and unconjugated NPs. Additionally, molecular analysis of the therapeutic advantages of rapamycin-loaded Tmab-conjugated NPs indicated enhanced downregulation of the mTOR signaling pathway, leading to increased cell death. In a 2D monolayer and a 3D tumor spheroid model, targeted multifunctional NPs have demonstrated remarkable bioimaging capabilities. As a result, one might expect that such a multimodal nanotheranostics technique will someday prove to be a valuable tool for better cancer management.[171] Besides, PEGylated liposomes linked with IONPs and L-IONP/DiR are promising as theranostic agents due to their dual *in vivo*

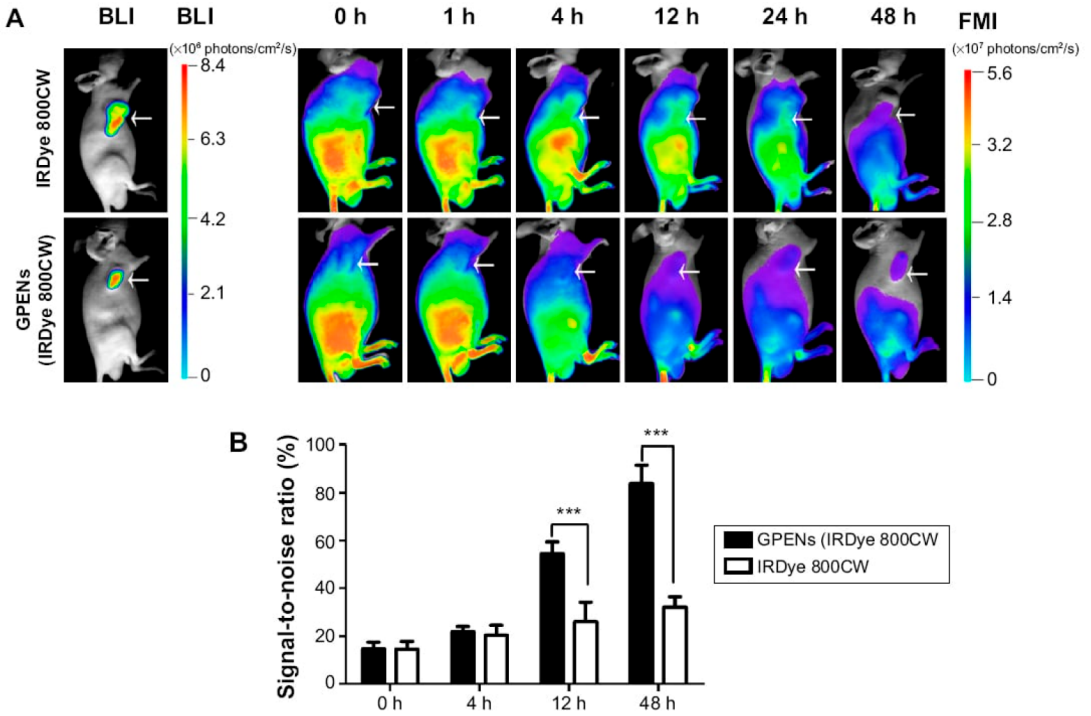

Figure 11. GPENs as a theranostic agent to enable real-time monitoring of treatment efficacy *in vivo*. (A) The biodistribution of GPENs. (B) Signal-to-noise ratio of GPEN fluorescence and free IRDye 800 CW. Adapted under CCBY4 from ref 174. Copyright (2015) DOVEpress.

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Table 1. Summarized Examples with the Role of Nanotheranostics for Solid Tumor Treatment

Nanotheranostics	Examples	Applications	Addressing problems	Refs
Magnetotheranostics	•Multifunctional nanorice	•Multimodal imaging	•Quicker delivery	137, 192, 193
	•WS2-IO@MS-PEG	•Contrast agents	•Increased tissue penetration	
	•MoS_2/Fe_3O_4 composite	•Hyperthermal killing	•Specificity toward cancer cells	
		•Drug delivery	•Good biofluid stability	
			•Minimal toxicity	
Plasmonic theranostics	•SERS nanoantennas	•High-contrast imaging systems	•Greater payloads	151, 152, 194−197
	•Gold nanoclusters	•Imaging and targeted therapy	•Quick endosomal escape	
	•Gold−silver nanoshell (Ag/Au-NS) with glucose oxidase	•Precise therapeutic efficacy	•Minimal photobleaching	
	•Au@Ag/Au-AAP nanoassemblies	•Photoacoustic imaging	•Effective site-specific theranostics	
	•mAb-GNP-miR491-Qdot construct			
	•Au DENPs covalently coupled with α-TOS			
Hybrid nanotheranostics	•SiNPs coupled with Alexa Fluor-488, iRGD peptide and dibenzocyclooctyl	•Antimitotic chemotherapeutics	•Selective targeting	198−201
	•EuGd-MSN-CPT	•Image-guided drug delivery	•Deliver insoluble drugs into cancer cells	
	•CS-MSNs	•MRI and fluorescence imaging		
Graphene theranostics	•Graphene nanosheets	•Image-guided tumor ablation	•Ease of surface modification and functionalization	202−205
	•Gd-NGO	•Contrast agent for MRI	•Increased biocompatibility	
	•Gd-NGO/Let-7g/EPI	•Chemoembolization therapy		
	•Pc-graphene nanoplatform	•Molecular imaging diagnosis		
Bioresponsive soft theranostics	•PEGylated liposomes linked with IONPs and infrared dye (L-IONP/DiR)	•Superparamagnetic MRI	•Increased treatment effectiveness	174, 206−208
	•PGN-L-IONP/DiR nanocomposite	•Fluorescence imaging	•Excellent tissue penetration capabilities	
	• GX1-conjugated poly(lactic acid) NPs encasing Endostar (GPENs)	•Real-time monitoring of treatment efficacy		
	•Pyrene polymer with an optical imaging dye	•Optical imaging applications		
Biomimetic theranostics	•Ferritin nanocages	•NIR fluorescence/photoacoustic/thermal multimodality imaging	•More specific targeting to cancer cells	209, 210
	•HSA@CySCOOH nanoplatform	•Photothermal tumor ablation	•High fluorescence intensity	
			•Good stability	
			•High water dispersibility	
			•Biodegradable and biocompatible	

imaging modes, superparamagnetic MRI, and fluorescence imaging in NIR.[172] To create a PGN-L-IONP/DiR nanocomposite that prevented the growth of MDA-MB-231 (breast) tumor cells, researchers loaded L-IONP/Dir with antihuman PGN635 monoclonal antibody (specific for phosphatidylserine, which is exposed in tumor blood vessel endothelial cells but not in normal tissue endothelial cells). MRI and optical imaging were used to diagnose the PGN-L-IONP/DiR activity.[171]

A potential nanotheranostic agent can be made of polymeric NPs coupled with Gd ions and biotinylated vascular endothelial growth factor receptor antibodies and loaded with the anti-HCC medication sorafenib. Several protein kinases, including receptor tyrosine kinases and serine or threonine kinases, are inhibited by this.[173] Du et al. developed a theranostic agent made of GX1-conjugated poly(lactic acid) NPs encasing Endostar (GPENs) and labeled with the near-infrared dye IRDye 800CW to increase colorectal tumor targeting and treatment effectiveness *in vivo*.[174] The *in vivo* fluorescent molecular imaging results showed that in mice with colorectal cancers GPENs more precisely targeted tumors than free IRDye 800CW (Figure 8). Additionally, bioluminescence imaging and immunohistology tests were used to assess the antitumor efficacy, which showed that GPENs had better antitumor efficacy on subcutaneous colorectal xenografts than other treatment groups. Thus, GPENs, a novel GX1 peptide-directed form of nanoscale Endostar, can be employed as a theranostic agent to enable real-time monitoring of treatment efficacy *in vivo* and permit more effective targeted therapy.[174]

Optical imaging is a noninvasive diagnostic method that enables the visualization of tissues using various techniques such as near-infrared (IR), fluorescent, and bioluminescent methods. In this approach, specific dyes are administered to the patient prior to imaging to facilitate the detection and analysis of tissues.[175] To enable the effective use of these dyes in nanotheranostics, it is crucial to employ various delivery strategies, including both chemical and physical methods. Chemical approaches involve conjugating the dyes with lipids or polymers, while physical methods focus on nanoencapsulation. One successful example involved the conjugation of a pyrene polymer with an optical imaging dye, resulting in a nanoparticulate formulation. This approach demonstrated excellent tissue penetration capabilities and significantly enhanced fluorescence intensity, offering improved performance for optical imaging applications[176] (refer to Figure 11).

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Table 2. Clinical Trials and Status

Clinical trial title	Interventions	Number enrolled	Age	Applications	Remarks	NCT number
GI-101 as a single agent or in combination with pembrolizumab, lenvatinib, or local radiotherapy in advanced solid tumors	GI-101 Pembrolizumab Lenvatinib Radiation: local radiotherapy	374	18 years and older	Targeted delivery with reduced off-target toxicity Used as imaging agents to visualize tumor lesions[214]	Assess the safety, tolerability, and toxicities of various agents The study is yet to enroll	NCT04977453
Methotrexate combined with immunotherapy during radiotherapy for solid tumors	Methotrexate tablets Anti-PD-1 monoclonal antibody Radiation: radiotherapy	50	18−85 years	Targeted delivery with reduced systemic toxicity Potentiated the impact of radiotherapy on tumor cells by the enhanced accumulation of radiation at the tumor site[215]	Primary outcomes verify the percentage population that has a response (complete or partial)	NCT05522582
Study of PD1 blockade by Pembrolizumab with stereotactic body radiotherapy in advanced solid tumors	Stereotactic body radiotherapy (SBRT)	117	18 years and older	Targeted and efficient delivery of Pembrolizumab Enhanced tumor response Enhanced the effects of SBRT[216]	Minimum of one dose constraint was observed in 52% of patients	NCT02608385
Local radiotherapy in combination with immunotherapy in advanced solid tumor patients	PD-1 blocking antibody	55	18−75 years	Targeted delivery to the tumor site Helped to overcome the immunosuppressive microenvironment Enhanced antitumor immune response[217,218]	The objective of the study is to reduce by 30% volume in at least a month The study has not posted a result	NCT05097781
ADC combined with hypofractionated radiotherapy, PD-1/PD-L1 and sequential GM-CSF and IL-2 for treatment of HER-2 positive advanced solid tumors (PRaG3.0)	ADC combined with radiotherapy, PD-1/PD-L1 sequential GM-CSF, and IL-2	55	18 years and older	Targeted delivery of ADC to HER-2 positive tumor cells Used as imaging agents to visualize tumor lesions[219]	An adverse event was observed, such as alopecia, fatigue, rash, and hepatic damage	NCT05115500
Radiotherapy combined with Irinotecan and Apatinib followed by PD-1 antibody and apatinib for advanced solid tumors	Irinotecan liposome Apatinib PD-1 antibody Radiation: radiotherapy	30	18−70 years	Targeted delivery of Irinotecan, Apatinib, and PD-1 antibody directly to the tumor site For synergistic effect[219,220]	Study is supposed to have its primary completion on February 2023	NCT04569916
Hypofractionated radiotherapy combined with PD-1 inhibitor sequential GM-CSF and IL-2 for the treatment of advanced refractory solid tumors (PRaG2.0)	Drug: PD-1 inhibitor Drug: GM-CSF Drug: IL-2 Radiation: hypofractionated radiotherapy	66	18 years and older	Targeted delivery to increase the drug concentration in the tumor microenvironment As imaging agents[221]	To a lesser extent, fatigue, rash, and decreased appetite were prevalent in various adverse events	NCT04892498
131I-L19SIP radioimmunotherapy (RIT) in combination with external beam radiation in patients with multiple brain metastases from solid tumors	131I-L19SIP radioimmunotherapy (RIT) in combination with whole brain radiation therapy (WBRT)	32	18 years and older	Improved the delivery of radioimmunotherapy agents across the blood−brain barrier Minimized systemic toxicity by selectively delivering radioimmunotherapy agents to the brain metastases[222]	Not available	NCT01125085
Study of RP-3500 in combination with standard radiation therapy in people with solid tumor cancer	RP-3500 Radiation: external beam radiotherapy (EBRT)	74	18 years and older	Enhanced the effects of standard radiation therapy Designed to overcome resistance mechanisms, allowing RP-3500 to remain effective in tumors that have become resistant to standard treatments[223]	The study is yet recruiting, and results are not available	NCT05566574

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Table 2. continued

Clinical trial title	Interventions	Number enrolled	Age	Applications	Remarks	NCT number
Radiation Therapy and sargramostim in treating patients with advanced solid tumors	Sargramostim Radiation: radiotherapy	N/A	18 years and older	Immunomodulated and enhanced efficacy of sargramostim in combination with radiation therapy[224]	Not available	NCT00091052
Phase 1 trial of MSC2490484A, an inhibitor of a DNA-dependent protein kinase, in combination with radiotherapy	MSC2490484A (M3814) Radiation: fractionated RT Cisplatin	52	18 years and older	-	Dose −300 mg BID Adverse event observed— nausea, vomiting, fatigue, and rash	NCT02516813
Study of NOX66 and external beam radiotherapy in patients with metastatic castration-resistant prostate cancer and other solid tumors	NOX66 Radiation: EBRT	100	18 years and older	Enhanced the effectiveness of NOX66, a sensitizer that enhances the effects of external beam radiotherapy on tumor cells	Currently enrolled in phase 1/2	NCT04957290
Study of AZD1390 and stereotactic body radiotherapy (SBRT) for people with metastatic solid tumor cancer	AZD1390 Radiation: SBRT	48	18 years and older	Enhanced the effectiveness of AZD1390, a DNA-PK inhibitor that sensitized tumor cells to the effects of SBRT[225]	Dose could be 8 Gy in past administration or 20/25 Gy as 5 fractions administered over 5 days	NCT05678010
Study of Avelumab-M3814 combinations	M3814 Avelumab Radiation: radiotherapy	57	18 years and older	Enhanced the antitumor immune response Selectively delivered Avelumab and M3814 to the tumor cells Simultaneously targeted DNA repair pathways[226]	Phase 1 trials are under progression. No result was posted	NCT03724890
CHEckpoint inhibition in combination with an immunoboost of external beam radiotherapy in solid tumors (CHEERS)	Nivolumab or Pembrolizumab or Atezolizumab Radiation: SBRT	99	18 years and older	-	The result is not available.	NCT03511391
GDC-0084 with radiation therapy for people with PIK3CA-mutated solid tumor brain metastases or leptomeningeal metastases	GDC-0084 Radiation: whole brain radiation therapy	36	18 years and older	As imaging agents[227]	Starting dose would be 45 mg daily, and the study focuses on determining the maximum lethal amount	NCT04192981

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BIOMIMETIC THERANOSTICS

Recent years have seen a substantial increase in interest in protein-based nanotheranostic drugs.[177−179] Therapeutic and diagnostic substances have been transported inside engineered protein nanocages.[180,181] Due to the proteinaceous structure of these nanocages, modifications can be made to both their internal and external surfaces. Drugs, aptamers, and contrast agents can be loaded onto the surface through internal surface modifications, while external surface modifications can facilitate ligand conjugation.[182] The pyruvate dehydrogenase multienzyme complex in *Bacillus stearothermophilus* produces naturally occurring protein nanocages (E2 nanocages), which are 24 nm in size.[183] These nanocages can be a flexible scaffold transporting theranostic drugs since they self-assemble from 60 monomeric units to produce a thermostable lattice structure.[183] Ferritin nanocages have become popular in cancer theranostics, similar to E2 nanocages. CD71, overexpressed in tumor cells, has a natural affinity for the ferritin-heavy (H) chain.[184,185] This unique property of ferritin can be used to find ferritin nanocages more specifically targeted to cancer cells, increasing the likelihood of effective theranostic drug delivery.[180,181] Other groups of protein-based nanotheranostics agents, including protein nanocages, also show great promise. Examples of effective theranostic agents include nanoradiopeptides and fluorescent peptide nanoprobes.[186,187] Additionally, researchers have created nanocomposites inspired by lipoproteins and shown theranostic potential in cancer treatment.[188] Recently, novel cancer nanotheranostics agents were created via drug-induced self-assembly of altered albumins.[189]

Rong et al. developed protein-based photothermal theranostics for imaging-guided cancer therapy.[179] In this study, a rigid cyclohexenyl ring was deliberately added to the heptamethine chain to create a heptamethine dye called CySCOOH, which has a high fluorescence intensity and good stability. The HSA@CySCOOH nanoplatform is particularly effective for NIR fluorescence/photoacoustic/thermal multimodality imaging and photothermal tumor ablation due to the covalent attachment of CySCOOH onto human serum albumin (HSA). *In vitro* and *in vivo* tests were conducted to systematically assess the theranostic potential of HSA@CySCOOH. Most intriguingly, complete tumor eradication was accomplished in mice with 4T1 tumors by intravenous injection of HSA@CySCOOH (CySCOOH, 1 mg/kg; 808 nm, 1.0W/cm^2 for 5 min). No weight loss, apparent toxicity, or tumor recurrence was noted. The practical application of this protein-based nanotheranostics for cancer photothermal theranostics is made more accessible by its high water dispersibility, lack of off-target cytotoxicity, good biodegradability, and biocompatibility in its as-prepared state.[179] Besides, along with whey, milk, and soy proteins, other proteins, like zein, gelatin, legumin, gliadin, elastin, and collagen, have also been employed as nanodrug/signaling agent carriers.[190,191] In addition, a recent revolutionary approach to semiconductor nanocrystal production that uses protein nanoreactors has shown promise as a cancer theranostic tool.[178] The nanoplatforms with their examples being employed for nanotheranostic applications in several biomedical engineering applications for treating solid tumors are listed in Table 1.

TRANSLATIONAL VIEW

With all the uncertainty and possible hurdles affecting the molecule's effectiveness, checking it in a living system before being marketed is crucial. In the initial research stage, animal models are incorporated to ensure various parameters such as safety, lethal dose, toxic dose, mechanism of action, etc. Wilmes et al. used dynamic contrast-enhanced MRI along with Axitinib in mice having a xenograft of a breast tumor.[211] This leads to a decrease in angiogenesis. A significant reduction in the tumor was observed just in 3 weeks. In a week, the scientist noted a decrement in the perfusion of tumors compared to the control.[211] Another study by Zhang et al. included the coadministration of PLGA and autophagy. Experimentation on mice concluded that tumor size in mice reduces to half compared to PLGA administration in just 20 days (refer to Table 2). This explains the effect of combination therapy in the diagnosis and treatment.[212] Das et al. designed a molecule with four moieties, including a targeting agent, methotrexate, fluorochromem, and a targeting agent.[213] The study concluded that in 24 h, the target accumulation of the drug was 19.14 and 8.62 times higher in human lung and breast cancer cells, respectively (in mice). It also facilitates the controlled release of methotrexate to promote a long-duration action.[213]

INTERPLAY OF KNOWN AND UNKNOWN FACTORS

Nanotheranostics represents a cutting-edge field at the intersection of nanotechnology and medical science, offering potential breakthroughs in diagnosing and treating solid tumors. Although it is an efficient strategy that may offer a more personalized and target-specific approach for cancer, it still has limitations that need to be addressed before successfully integrating this technology into the clinics. Moreover, the interplay of known and unknown factors in nanotheranostics is crucial for its success in effectively combating solid tumors. Enzymatic degradation, a significant limitation in nanotheranostics, hampers its affinity toward the target.[228] Researchers have used LXL-1 aptamers as a nanotheranostics tool to precisely bind with the target molecule with high affinity and stability in treating triple-negative breast tumors. Still, the aptamer was easily degraded by nucleases, thus decreasing its bioavailability at the tumor site.[229,230] Similar enzymatic degradation was also seen with platelet-derived gold-factor-aptamers conjugated with AuNPs intended to target a unique protein on the breast cancer cell line.[231] Also, the 26-mer G-rich DNA aptamer selectively targets the nucleolin receptor in certain solid tumors but is still liable to enzyme degradation.[232] Hence, nanotheranostics approaches for solid tumors must still be enhanced and integrated into aptamer-based targeted diagnostic tools.

In nanotheranostics, modified virus-like particles are undoubtedly used extensively to target solid tumors due to their ability to escape the endosomes before lysosomal degradation, thereby increasing drug bioavailability.[233] However, most virus-like particles demonstrate tropism to heparin sulfates, which restricts their application as targeted nanotheranostics. However, some virus-like particles exhibit natural tropism to specific organs or tissues, such as HEV-like particles for hepatocytes,[234,235] but it is also associated with a limitation of the eliciting innate immune response because of the presence of viral proteins that get easily absorbed by the dendritic cells.[236] Therefore, despite the advantages associated with virus-like particles, such as adaptability, effective cell entry, biocompatibility, absence of endosomal sequestration, and multivalency, this nanotheranostics tool is still in the preliminary phase and requires animal model validation. Many

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studies have also been done with light-sensitive nanotheranostics for treating solid tumors. However, despite their biocompatibility and light-sensitive ability, this tool's primary challenge is the drug field's poor pharmacokinetics.[237,238] Additionally, low permeation of light-sensitive drugs via nanotheranostics into the solid tumor is associated with phototoxicity, which stays in the systemic circulation for several weeks, which limits its use as a nanotheranostic.[239,240] Photosensitive nanotheranostics also pose the challenge of photobleaching, making room for more improvements. Critical challenges associated with metallic nanotheranostics[241−243] include retarded degradation and high cytotoxicity. In contrast, with nonmetallic nanotheranostics, the premature release of payload, with biological nanotheranostics, is a high-affinity binding with target proteins and quantum-dot-based nanotheranostics in rapid first-pass metabolism and clearance.[244]

Besides, most of the nanotheranostics used in solid tumor studies are intended for targeted therapy and diagnostics; current research in nanotheranostics mainly focuses on strategically integrating therapeutic and imaging techniques that ultimately limit the therapeutic efficacy locally at the tumor site while enhancing drug absorption. One major challenge for nanotheranostics assessment in tumor models is to simulate actual clinical conditions that must be addressed to restrict cancer progression and improve efficacy. Many studies used QDs coencapsulating a cytotoxic drug in lipid nanoparticles as a theranostic tool for a xenografted murine melanoma model, which showed escalated blood circulation time.[245] Also, studies formulating surface-modified temperature-sensitive liposomes encapsulating chemotherapeutic agents and an MRI agent clearly showed enhanced drug release at the target site of the gliosarcoma.[246] These few examples of research studies show a tremendously promising field for developing better nanotheranostics for solid tumors. Nanotheranostics with adequate auxiliary systems can accelerate diagnostic analysis and efficient treatment, improving patient compliance and survival. Nanotheranostics may also become an invaluable tool in the upcoming and future era of personalized therapeutics to choose the more appropriate treatment regimens, predict therapeutic responses, and track the patients' clinical development. Moreover, mastering the cellular and molecular connection in nanotheranostics with solid tumors and being competent at combining numerous modalities into one system remain a significant challenge that needs a potential answer. Overall, this discovery should undoubtedly pique pharmaceutical firms' attention very shortly for developing efficient theranostic nanoplatforms and the eventual release of such revolutionary nanotheranostics onto the market.

CONCLUSION

Cancer has remained one of science's most vexing mysteries for centuries due to the variety of its etiologies. A complete cure for the disease is still improbable, despite the commendable increase in cancer patient survival rates brought about by better therapeutic and diagnostic procedures. Therefore, research is required to find cutting-edge cancer treatment and diagnosis methods. One of the advanced techniques, theranostics, offers a two-pronged advantage in cancer management. In light of nanotechnology, this integrated approach has become incredibly relevant. The tumor targeting and selectivity of NPs make them promising for cancer therapy. These NPs can offer protection from the immune system and increase their blood circulation times via surface modifications. To increase the effectiveness of NPs in targeting tumors, active targeting ligands can be added to their surfaces. NPs can be employed as functional building blocks to create "all-in-one" delivery systems that incorporate all necessary functionalities. All-in-one NPs can treat cancer by combining therapy, diagnosis, and monitoring procedures. Theranostic qualities can be tailored in NPs to create nanotheranostic agents by loading them with a mixture of therapeutic drugs and diagnostic probes. These nanocomposites can be customized for targeted drug delivery and are valuable tools for obliterating cancer cells while concurrently evaluating the drug's efficacy. Nanotheranostic agents have become a wise strategy to identify the "route and reach" of the drugs and coordinate cancer treatment.

Despite the potential of nanotheranostics, successful clinical translation faces numerous obstacles. The scientific research community is working hard to get these nanotheranostics into clinical trials. Optimizing tumor accumulation/retention, the biodistribution of administered NPs and understanding how these nanomaterials interact with biological systems are currently critical challenges for all forms of cancer. The material utilized to develop the nanoplatform and its inherent ability to interact with the tumor microenvironment may be connected to our observed active and passive transportation differences. However, a promising future for polymeric-, metallic-, and lipid-based nanosystems combining diagnostic and therapeutic functions is anticipated. For this, noninvasive imaging techniques are strongly required to assess specificity receptor binding and internalization mechanisms of the nanosystems into the tumor cells. To accomplish this, it is necessary to develop a thorough understanding of how they interact, including a safety evaluation, from a biological standpoint. On the other hand, pharmaceutical companies must conduct clinical trials and introduce this nanotheranostics into the market to succeed. As was covered in this article, there are many ways to understand the function of nanotheranostics, particularly in cancer treatment.

In conclusion, the interplay of the known and unknown factors in conjugated nanoparticle-based theranostics for solid tumors is a dynamic process that requires consistent ongoing research and dedication. While significant progress has been made, further exploration and understanding of the unknown factors will drive the next wave of innovations in cancer diagnosis and therapy. Additionally, more effort should be put into scaling up the synthesis, evaluating the toxicity over time, and creating regulated guidelines for nanotheranostics. Moreover, as we continue to unravel the mysteries surrounding these nanoscale agents, the future of cancer treatment looks increasingly promising, offering renewed hope for patients and healthcare providers alike.

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Notes

The authors declare the following competing financial interest(s): J. Conde is a co-founder and shareholder of TargTex S.A. Targeted therapeutics for Glioblastoma Multiforme. R.P. is a part of national and international patents related to gold, silica, and liposome nanoparticles. All the other authors confirm no competing interests.

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