Nanomaterials in Cancer Therapy

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This entry analyzed the different roles of nanomaterials, such as contrast agent and dose enhancer, in biomedical imaging and cancer therapy. Moreover, the review discussed the underlying mechanisms of nanomaterials including physical, chemical, and biological mechanisms. Some new applications of nanomaterials as theranostic agents are explored. Through a thorough understanding of the recent advances in nanomaterial application in biomedical imaging and cancer therapy, we identified new directions for the optimization and clinical transformation of nanomaterials.

Keywords: Nanomaterials ; gold nanoparticles ; medical imaging ; cancer therapy ; contrast agent ; nanoparticle-enhanced radiotherapy ; radiotherapy

1. Introduction

In the past 10 years, there have been advances in nanomaterials, such as the development of hundreds of nanoparticles (NPs)-based probes for molecular imaging. The use of NPs has enhanced almost all major imaging techniques, particularly magnetic resonance imaging (MRI), positron emission tomography (PET), and optical imaging. Some of the important milestones are the use of iron oxide NPs in T1 weighted and/or T2 weighted MRI, the design of radioisotope chelator free (use of radioactive metals that form a stable interaction directly with the surface or core of the NP) particles for PET, and the development of fluorescent NPs such as carbon dots and upconverting NPs [1]. On the other hand, novel types of optical nanoprobes, such as persistent luminescence nanoparticles (PLNPs), are being developed to take advantage of long lasting near-infrared (NIR) luminescence capability [2]. This allows optical imaging without constant excitation and autofluorescence [3].

The latest research and advancement in nanotechnology lead to the development of various NPs for diagnostic and therapeutic applications. Even though clinically, the number of usages of NPs is limited by the complex demands on their pharmacokinetic properties, nanodiagnostics improve the understanding of important physiological principles of various diseases and treatments. On the other hand, NPs are widely used in the clinic for therapeutic purposes. Therapeutic NPs improve the accumulation and release of pharmacologically active agents at the pathological site, which overall, increases therapeutic efficacy and reduces the incidence and intensity of the side effects. NPs hold great promise for integrating diagnostic and therapeutic agents into a single NP for theranostic purposes. A good example would be monitoring biodistribution and target site accumulation, quantifying and visualizing drug release, and longitudinally assessing therapeutic efficacy. Theranostic NPs can be used for personalized nanomedicine-based therapies [4]. Nanoparticles' intrinsic unique magnetic or optical properties make their application ideal for various imaging modalities. Nanoparticles make excellent contrast agents due to their high sensitivity, small size, and composition. Nanoparticles are often conjugated with suitable targeting ligands on the surface of the particles. Multifunctional NPs can be developed by incorporating various functional materials, and this enables multimodal imaging and therapy simultaneously, also known as theranostics [5].

Although each of the imaging and therapy modalities has improved significantly over the past few years, there are caveats in nanomaterial application that are impeding its application. For example, no single molecular imaging modality can offer all the required data fully characterizing the properties of an administered agent. Each imaging modality has a major shortcoming, such as MRI has high-resolution but low sensitivity, optical techniques have limited tissue penetration, and radioisotope imaging techniques have relatively poor resolution but high sensitivity. Combining multiple imaging techniques can enable these applications to complement one another, and a multimodal imaging agent becomes the key to enhancing those imaging systems [6].

2. Cancer Therapy

Cancer therapy is the technique of inhibition or irradiation of cancer cells. There are several techniques available and each one is more beneficial to one type of cancer treatment than others. Nanomaterials offer significant enhancement to many of the cancer therapies and they are discussed below:

2.1. Photothermal Therapy

Photothermal therapy is a hyperthermia-based cancer therapy. The goal of this therapy is to destroy tumour tissue while avoiding excessive heating of normal tissues. Biological tissue lacks NIR-absorbing chromophores. The use of laser wavelength in the 'tissue optical window' (700–1000 nm) minimizes tissue heating, while Au NPs have strong and tunable absorption in the NIR region. Therefore, Au NPs and NIR can be used to facilitate selective heating of tumours with NPs [7]. Gold nanoparticles with thiol and amine groups can be functionalized with targeted antibodies or drug products. Colloidal gold exhibits localized plasmon surface resonance. It can absorb light at specific wavelengths, which makes them useful for hyperthermic cancer treatment application. A gold nanoparticle's localized plasmon surface resonance can be changed with the modification of the particle's shape and size, which alters its photothermal and photoacoustic properties, allowing utilization of different wavelengths of light. Its nanosize allows the particle to localize in the tumour through passive distribution and excrete through the urinary system [8]. One of the major problems with PTT is that heat distribution is often heterogeneous throughout the tumour, which leaves part of the tumour untreated. A new idea was proposed which uses silica gold nanoshells to deliver fractionated PTT [9]. Gold-based NPs are the main mediator of PTT because they offer biocompatibility, efficient light to hear conversion, ability to be tuned to absorb NIR light which penetrates tissue more deeply, a small diameter that enables tumour penetration, and simple gold thiol bioconjugation chemistry for the attachment of the desired molecule. Nanoshells, nanocages, nanorods, and nanostars are the most common nanomaterials as photothermal transducers. The majority of Au NPs have been designed to maximally absorb within the first NIR window, which can safely penetrate 2–3 cm of tissue [10]. A PET-based nanoplatform was introduced to quantitatively correlate to the heat generation of plasmonic NPs with their potential as a cancer-killing agent. Heat generation was evaluated in human tumour xenografts in mice using 2-deoxy-2-[F-18]-fluoro-D-glucose (^{18}F—*FDG*) PET imaging. The platform was validated by quantifying the photothermal efficiency of the NIR silica gold nanosphere and benchmarked it against the solid Au NPs. The results showed the heat generation of the resonant gold nanospheres (in vitro and in vivo) performed better compared to the control. It also showed PET could reliably be used to monitor early treatment response in PTT [11].

In PTT, the temperature of the tumour is raised above 42 degrees Celsius to destroy the cancer cells. A light-absorbing material or photothermal agent must be introduced into the tumour to improve the efficacy and selectivity of the energy to heat transduction. Even though gold is the most employed agent in PTT, magnetic NPs are a good alternative. Magnetic NPs formed by iron oxide can be used in combination with other substances or used by themselves as photothermal agents. They can be directed to the tumour site magnetically and their distribution in tumours and other organs can be imaged. Their molar absorption coefficient in NIR is low when they are used alone. However, this can be mitigated by clustering of the NPs. They can also be designed to release a drug upon heat generation, which can be beneficial for combination therapy of PTT and chemotherapy [12].

Polymer-based NP systems have been investigated to overcome some of the limitations associated with traditional inorganic NPs. Some of the materials that have been investigated for this purpose include polyaniline, polypyrrole, polydopamine, and poly-(3,4-ethylene dioxythiophene): poly(4-styrene sulfonate). They are often conjugated with ligands for targeting ability. A specific set of requirements should be met for NPs to be an ideal candidate for PTT, such as suitable size and uniform shape, good dispersibility in aqueous solution, respond to light in NIR range 650–950 nm to prevent damage to surrounding healthy tissue, sufficiently photostable to ensure adequate diffusion time to reach tumour before losing their photosensitivity, and exhibit low or no cytotoxicity in a living system. Current available PTT enabling agents mainly comprise metal NPs such as gold, palladium, silver, germanium, and carbon-based NPs. Some of the polymer-based NPs systems are listed in Table 1 below [13].

Table 1. Polymer-based nanoparticle system for PTT [13].

Polymer	Configuration	Testing Stage

	NPs	
	F-127 Conjugated NPs	
	Silver core, Polyaniline shell (ICG-Ag@PANI)	
Polyaniline	NPs with lanreotide and methotrexate (LT-MTX/PANI NPs)	In vitro and in vivo
	WS core, polyaniline shell with hyaluronic acid and chlorin e6 (Ce6)	
	Polyaniline and cisplastin within folate-poly (ethylene glycol)-distearoylphosphatidylcholine (FA-PEG-DSPE), cRGD[cyclic (Arg-GLY-Asp-D-Phe-Lys)]-PEG-DSPE, and lecithin conjugates dubbed FA/cRGD-PNPs	
Polydopamine	Dopamine-melanin colloidal nanospheres	In vitro and in vivo
	PEGylated polydopamine NPs conjugated with ICG (PDA-ICG-PEF) loaded with DOX	In vitro
	Pegylated NPs loaded with 7-ethyl-10-hydroxycamptjotheticin (SN38)	In vivo
	DOX encapsulated with DSPE-PEG micelles coated with polydopamine	In vitro and in vivo
	Fe(3)O(4) core polydopamine coated nanoshell	In vitro
	Polydopamine coated gold nanorods	In vitro
	Polydopamine coated gold/silver NPs	In vitro

Polypyrrole	Base NPs	In vitro and in vivo
	Base NPs	In vitro
	Spindle-like hollow polypyrrole nanocapsules (PPy HNCs) loaded with DOX	In vivo
	Ppy and rapamycin loaded into liposomes conjugated with trastuzumab (LRPmAB)	In vitro
TBDOPV-DT	D-A conjugated polymer (TBDOPV-DT), with 2,2-bithiophene serving as a donor and thiophene-fused benzo-difuran dione-based oligo (p-phenylenevinylene) as an acceptor (TBDOPV-DT NPs)	In vitro and in vivo
PEDOT:PSS	PEGylated PEDOT:PSS NPs (PDOT:PSS-PEG)	In vivo
	PEDOT: PSS-PEG loaded with DOX, SN38, and Ce6	In vitro
	Magnetic NPs with PEDOT: PSS Cyanine7 (Cy7), and 2-deoxyglucose (2-DG)-polyethylene glcol (MNP@PES-Cy7/2-DG)	In vitro and in vivo
	Magnetic NPs with PEDOT: PSS coating	In vivo

In PTT, red blood cell-coated NPs show improved efficacy with a faster decrease in tumour volumes and a higher survival rate than bare NPs. It is speculated that red blood cell NPs inherit the photothermal conversion effect from inner cores and the long blood retention from the red blood cell coating. One study showed that the combination of biodegradable, natural, and nontoxic melanin NPs extracted from living cuttlefish and red blood cell membrane have significantly higher PTT efficacy. Au NPs encapsulated with the antitumour drug paclitaxel-coated by anti-EpCam antibodies-modified red blood cell membranes show increased cancer-targeting ability due to anti-EpCam antibodies. Paclitaxel can be released when the membrane is destroyed by the heat generated from the Au NPs under laser irradiation to yield the anticancer effect [14].

2.2. Photodynamic Therapy (PDT)

Photodynamic therapy is a form of light therapy that uses molecular oxygen, visible light, and photosensitizers (PS) to destroy cancer cells and pathogenic bacteria. Photodynamic therapy is noninvasive and selectively cytotoxic to malignant cells. It causes direct tumour cell damage by apoptosis necrosis and autophagy. The photosensitizer is distributed directly into the tumour site or systematically via the vascular system. In the presence of molecular oxygen, light at a specific wavelength is applied in PDT, followed by the production of reactive oxygen species (ROS), which results in oxidative damage of the intracellular elements within the cell. This leads to cancer cell death. When PS targets the vascular system of the tumour, it results in hemostasis, vessel constriction, and breakdown. This ultimately leads to a decrease in oxygen and nutrient supply to the tumour, which eventually results in tumour cell death. Gold nanoparticles are primarily used in PDT [15]. Porphyrins have been approved for the treatment of cancer in PDT. They have low physiological solubility and lack of selectivity toward tumours, which is not efficient. Nanoparticles can be used to transport porphyrins. Silica NPs (80 nm) coated with xylan–TPPOH conjugate was studied for such purpose and showed significant phototoxic effects from post-PDT ROS generation, and stronger cellular uptake in the human colorectal cancer cell line. They showed high anticancer efficacy [16]. The dual specificity of PDT relies on the accumulation of PS in tumour tissue and localized light delivery. Tetrapyrrole structures such as bacteriochlorins, porphyrins, chlorins, and phthalocyanines with functionalization have been widely investigated in PDT. Several compounds have already received clinical approval. Photosensitizers conjugated to antibody, proteins, peptide, and other ligands with specific cellular receptors are used in targeted PDT. Nanotechnology has also been widely used for targeted delivery. Fullerene-based PS, titania photocatalysis, and the use of upconverting NPs to increase light penetration into tissue have been studied [17]. Table 2 is a list of several nanoplatforms for PDT and their advantages [18].

Table 2. Nanoplatforms for PDT and their advantages [18].

Nanoparticle Platform	Advantages
Passive PDT PS tumour drug micelles and Liposomes	Enhanced tumour uptake and improved phototoxicity
Dendrimer encapsulated NPs	High loading drug
Metal oxide NPs	High loading capability, biocompatibility, easy surface modification
Immuno NPs	The highly specific molecule, improved drug release within the desired cell
Quantum dots	Large absorbance cross-section and size-tunable optical properties

To achieve synergistic chemiexcited photodynamic starvation therapy against tumour metastasis, a biomimetic nanoreactor was developed. Photosensitizers on the hollow mesoporous silica NPs were excited by chemical energy in deep metastatic tumour tissue to generate singlet oxygen, and then, glucose oxidase catalyzed glucose into hydrogen peroxide in PDT. This blocked nutrient supply for starvation therapy and provided hydrogen peroxide to synergistically enhance PDT [19]. Photosensitizer chlorin e6 (Ce6) and the ferroptosis inducer erastin were self-assembled into a novel supramolecular Ce6-erastin nanodrug though bonding and π−π stacking. Ferroptosis with nanodrug enhances anticancer actions by relieving hypoxia and promoting ROS production [20].

2.3. Chemotherapy

Chemotherapeutic agent DOX is a member of the anthracycline class. It is heavily used in many clinical cancer therapies. It is also one of the most used chemotherapeutic drugs for the treatment of breast cancer. Paclitaxel is another popular chemotherapeutic agent used in breast cancer. Other commonly used chemotherapy regimens are cisplatin, tamoxifen, trastuzumab, and docetaxel. The efficiency of the drug increases significantly with targeted drug delivery. Nanoparticle-based carriers are often conjugated to them for targeted delivery. Some of the NPs that are used in chemotherapy for breast cancer are polymer-based NPs, liposomal NPs, metal-based NPs (Au NPs, SPIONP), carbon-based NPs, mesoporous silica NPs, and protein-based NPs [21]. Nanoparticle vehicles are currently in clinical use and some are

undergoing clinical investigation for anticancer therapies, including dendrimers, liposomes, polymeric micelles, and protein drug NPs. There are many new NPs drug formulations in development and undergoing early and late phase clinical trials, including several that utilize active targeting or triggered release based on environmental stimuli. A variety of NP formulations have been approved by the FDA and EMA for the treatment of a wide range of cancers. Some examples are pegylated liposomal doxorubicin and liposomal daunorubicin, which are available in the United States. Nonpegylated liposomal doxorubicin is approved in Europe. Nab-paclitaxel is an FDA- and EMA-approved therapy using NP albumin-bound particles [22]. Various types of proteins and small peptides are often conjugated to the surface of NPs to improve the selectivity of chemotherapeutic drugs. Serum glycoprotein is one of the targeting ligands used with NPs in chemotherapy drug delivery [23]. The antimalarial agent chloroquine can reduce the immunological clearance of NPs by resident macrophages in the liver, leading to increased tumour accumulation of the nanodrug [24].

Gold nanoparticles have high stability, surface area-to-volume ratio, surface plasmon resonance, and multifunctionalities. The nontoxic, nonimmunogenic nature, high permeability, and retention effect of Au NPs provide additional benefits by enabling penetration and accumulation of the drug at tumour sites. DOX-BLM-PEG-Au NPs and EpCAM-RPAnN are two Au NP carriers that have high potential to be used in chemotherapy [25]. Cisplatin is a genotoxic agent that can be used alone or in combination with radiation or other chemotherapeutic agents. It is used in chemotherapy for a broad range of cancers. However, the agent is limited by the intrinsic and acquired resistance, and the dose to normal tissue. It shows little selectivity for tumour vs. normal tissue, which leads to toxicity. Nanoparticles can be used to deliver cisplatin to reduce toxicity. Some organic NPs that can be used to transport cisplatin are liposomes, polymeric NPs, polymeric micelles, and dendrimers. Some inorganic NPs are Au NPs, ferromagnetic NPs, and mesoporous silica NPs. Some hybrid NPs are CNT, nanoscale coordination polymers, and polysilsesquioxane NPs [26].

Organic NPs are a popular choice for chemotherapeutic drug delivery. They can increase the circulation half-life and tumour accumulation of a drug. Combination chemotherapy is used in the treatment of a broad range of cancers. Nanoparticles are essential to delivering many of these drugs to the target site and also provide a theranostic platform for multifunction [27]. Multidrug-loaded NPs formulation consists of different classes of therapeutic agents. It has been studied for breast cancer therapy in preclinical breast cancer models. One example would be polymer lipid hybrid NPs for coencapsulated DOX and mitomycin C. It has demonstrated its efficacy in the human breast cancer model, including multidrug resistance cells. Multidrug-loaded NPs micellar formulation was also developed for the delivery of three drugs: paclitaxel, 17-AAG (Triolimus), and rapamycin. They were evaluated on MDA-MB-231 tumour-bearing mice [28]. Hypoxia promotes the invasiveness of tumour cells and chemoresistance. Tumour-associated macrophages (TAMs) reside in the hypoxic region to promote proliferation and chemoresistance. Nanoparticles Mn with high reactivity toward hydrogen peroxide for the simultaneous production of and regulation of pH can affectively alleviate tumour hypoxia by targeted delivery of

to the hypoxic area. It was conjugated to DOX and significantly increased the apparent diffusion coefficient value of breast cancer and inhibited tumour growth [29]. A novel carrier, targeting nanomicelles for synchronous delivery of curcumin and baicalin, was introduced, which could effectively overcome tumour resistance. Mannose binds to CD206 receptors on the surface of tumour-associated macrophages, subsequently increasing the number of nanodandelions engulfed by tumour-associated macrophages. To increase tumour cellular uptake, oligomeric hyaluronic acid can also be used as a targeting material. Nanodandelions can easily enter tumour tissue through the vascular barrier due to their small size. Effective antitumour activity and reduced side effects were confirmed in antitumour experiments in A549 tumour-bearing mice [30]. Sustained-release characteristics of NPs may aid the effectiveness of chemotherapy by maintaining drug concentrations at the tumour site for longer durations. Nanoparticles can increase penetration and accumulation of the inhaled drug in tumour tissue and cells. This yield improved antitumour activity compared to the free drug. These characteristics make them suitable for chemotherapy for lung cancer [31].

2.4. Immunotherapy

During recent decades, cancer immune therapy has made significant progress with the improvement in nanotechnology. Immunotherapy is a therapy based on stimulation or activation of the patient's immune system to recognize and destroy cancer cells [32]. Understanding how to increase the response rate to various classes of immunotherapy is to improving cancer treatment efficacy and minimizing adverse side effects. There are five classes of cancer immunotherapy: lymphocyte-promoting cytokines, agonistic antibodies against co-stimulatory receptors, checkpoint inhibitors, engineered T cells such as CAR T and T cell receptor (TCR) T cells, and cancer vaccines. Nanoparticles can be used to target T cells in the blood or transport mRNA to the cancer cell, or transport other vaccines in immunotherapy [33]. Nanoparticle systems have shown to be a promising tool for effective antigen delivery. The antigen is generally in peptide form that can stimulate an adaptive immune response. For conditioning a robust and long-lasting adaptive immune response, stimulation of the

innate immune system through natural killer cells is necessary. Therefore, an adjuvant that works to recruit natural killer cell response is vital for effective vaccination. Table 3 summarizes the different antigens being studied for different cancer treatments and their delivery NP conjugate [34].

Table 3. Nanoparticle vaccine delivery for various cancer [34].

Cancer Type	Nanoparticles	Antigen
Melanoma	Poly(lactic-co-glycolic acid) (PLGA) NPs	Ag, Poly(I:C)
	Liposome	TRP2, α GalCer
	CNT	α CD40, CpG
	Cowpea mosaic virus (CPMV) NPs	Empty Cowpea mosaic virus (eCPMV)
Non-small cell lung cancer	L-BLP25 liposome	MUC1
Breast cancer	PLGA-PEG	Ovalbumin (OVA), Monophosphoryl lipid A (MPLA), CpG
Prostate cancer	Virus-like particle	Polyethylenimine-stearic acid (PSA)
Cervical cancer	Tumour virus vaccine	HPV

An adjuvant is a molecule that increases immunogenicity. They sometimes are lacking in tumour antigens when presented alone. Commonly used adjuvant in cancer treatment are 3-O-desacyk-4′-monophosphoryl lipid A (MPLA), CpG oligodeoxynucleotides (ODNs), lipopolysaccharide (LPS), polyinosinic:polycytidylic acid (poly I:C), and agonists of the stimulator of IFN genes (STING). When they are internalized in antigen-presenting cells with tumour antigens, they promote anticancer immune response [35]. Nanoparticles have a multifaceted role in modern immunotherapy. They can reduce tumour-associated macrophages and act as a tumour suppressor agent, selectively knockdown Kras oncogene addiction by the nano-Crisper-Cas9 delivery system, and serve as an efficient alternative to the chimeric antigen receptor [(CAR)-T] [36]. Immunotherapy is one of the effective modalities for cancer treatment. Targeting the tumour environment along with the immune system is a viable strategy to use for cancer treatment. Systematic delivery of immunotherapeutic agents to the body using NP delivery is of great importance. Liposomes, Au NPs, polylactic-co-glycolic acid (PLGA) NPs, micelles, iron oxide NPs, and dendrimers are widely used for immunotherapy. Polymeric NPs are the most commonly used ones in immunotherapy where PLGA is an FDA-approved polymeric carrier. Table 4 below lists the commonly used NPs used in immunotherapy, their therapeutic agent conjugate, target, function, and studied tumour model [37].

Table 4. Nanoparticle used in immunotherapy [37].

NP Materials	Therapeutic Agents	Target	Function	Tumour Model

	AUNP12 anti-PD-1 peptide	Tumour cells	Blockage of PD-1/PDL-1 pathway	4T1 Subcutaneous tumour
PLGA-based NPs	Trastuzumab	Human epidermal growth factor 2 (HER2)	GER2 degradation and antibody-dependent cell-mediated cytotoxicity	In vitro HER2 Positive breast model
	Pam3CSK4 and α-CD40-mAb	CD40	T cell response	B16-OVA Subcutaneous tumour
	SB505124 TGF-β 1 inhibitor	Tumour specific cytotoxic T-lymphocyte CTLs	Block TGF-β Signal and promote CD8 + T cell infiltration	E.g7-OVA Subcutaneous tumour
Liposomes	Curdlan and mannan	Cytosol of DCs	Activation of DCs via Th1 cytokine production	DC2.4 in vitro model
	Stimulator of interferon genes (STING) agonists and c GAMP	Tumour microenvironment (TME)	Proinflammatory gene induction and production of immunological memory	B16-F10 Lung metastatic tumour
	Pyranine antigen	Cytoplasm of DCs	Antigen-specific cellular immunity	C57BL/6 intradermal immunized mice
Micelles	NLG919/IR780	Lymph node	Suppression of growth of tumour margin in primary tumours	4T1 subcutaneous tumour
	ROS inducing ZnPP PM/PIC	Tumour-associated macrophages (TAMs)	Activation of NK cells and T lymphocytes	B16-F10 Subcutaneous tumour

AuNPs	OVA peptide antigen/CpG adjuvant	Dendritic cells	Induce systemic antigen-specific immune response	B-16 OVA Subcutaneous tumour
	α-PDL1	Tumour cells	Imaging and tumour reduction	Colon cancer Subcutaneous tumour
Iron Oxide NPs	Superparamagnetic	DCs and macrophages	Immune cell activation and cytokine production	CT2 Subcutaneous tumour
	Ferumoxytol	Macrophages	Increased caspase-3 activity and proinflammatory Th1 response	MMTV-PyMT Mammary tumour
Dendrimers	mAbK1/PTX	Tumour cells—mesothelin receptor	Specific binding and antitumour activity	OVCAR3 Subcutaneous tumour
Artificial exosomes	DEC205 monoclonal antibody	Dendritic cells	Targeting to DCs	In vitro studies-DCs

Cyclic dinucleotides (CDNs) is a potent stimulator of the interferon receptor (STING) agonist. Its efficacy is limited to micromolar concentration due to the cytosolic residence of STING in the ER membrane. Biodegradable poly (beta-amino ester) NPs were introduced to deliver CDNs to the cytosol, which leads to robust immune response > 100-fold lower extracellular CDN concentration in vitro. This NP-mediated cytosolic delivery for STING agonists synergizes with checkpoint inhibitors and has the potential for enhanced immunotherapy [38]. A new strategy of cancer immunotherapy using plant virus-based NPs was proposed. In vaccine development, plant virus has already been utilized extensively. Successful employment of plant viruses in cancer treatment has been observed using hibiscus chlorotic ringspot virus, tomato bushy stunt virus, and red clover necrotic mosaic virus. Plant viruses offer the advantage of uniformity concerning shape and size and ability to self assemble into highly repeating nanostructures. They also exhibit structurally defined chemical attachment sites, cargo capacity, and tolerance against high temperature and pH [39]. Metallic NPs also have high potential in immunotherapy. Several metallic NPs such as Au NPs have been studied to be used with several immunotherapeutic agents such as ovalbumin (OVA). Metallic NPs have also shown to improve antitumour cytotoxic T cell response. Metallic NPs have advantages which can be utilized with combination therapy of immunotherapy and PTT [40]. Elimination or reprogramming of the immune-suppressive tumour microenvironment is a major challenge in immunotherapy. Immune checkpoint inhibition targets regulatory pathways in T cells to enhance tumour response and has been the most successful method in immunotherapy. Some FDA-approved immune checkpoint agents are ipilimumab against CTLA-4, and pembrolizumab and nivolumab against PD-1. Lipid-based NPs are generally used to transport these materials to the target site [41]. A study showed that R848-loaded *β*—cyclodextrin NPs can efficiently be delivered to tumour-associated macrophages in vivo to macrophages to acquire an antitumourigenic M1-like phenotype. The functional orientation of the tumour immune microenvironment toward an M1 phenotype was achieved through the administration of CDNP-R848 in multiple mouse models. An improved immune response rate was observed when combined with immune checkpoint inhibitor anti-PD-1 [42]. Exosomes are nanosized particles secreted from most cells. This allows crosstalk between cells and their surrounding environment through cargo transfer. Tumour cells also secrete exosomes, known as tumour-derived exosomes. They have tumour modulation activity and can affect the tumour microenvironment and antitumour response. Their immunological activity influences both innate and adaptive immune systems, including regulatory T-cell maturation, natural killer cell activity, and anti-inflammatory response. Their characteristics allow them to be used for metastasis lung cancer treatment [43].

3. Conclusions

Recent advances in nanotechnology have resulted in great progress of synthetic techniques, which benefit from the design of many nanomaterials, such as nanoparticles, nanocages, nanodiamonds, nanoshells, and nanotubes. These nanomaterials can act as very effective contrast agents in various medical imaging modalities and provide a large number of options in modern cancer therapy. The nanomaterials allow delivery of many drugs to target sites that otherwise would not be possible and provide a fundamental basis for some cancer therapy that is showing promising clinical outcomes. It is expected that continuous discovery in nanotechnology will significantly influence future cancer therapy and medical imaging. However, some of the limitations of nanomaterials as drug carriers, contrast agents, and sensitizers, such as cytotoxicity and nonbiodegradability, should be studied further in order to minimize the side effects on humans.

For the transition of nanomaterial applications in biomedical imaging and cancer therapy into commercial clinical practice, it can be seen that many in vitro and in vivo studies have shown promising results. However, numerous challenges, such as physicochemical properties, drug metabolism, cytotoxicity and biocompatibility, pharmacokinetic screening, surface engineering, in vivo efficacy, nanomaterial uptake, immunogenic issues, and preparation costs, still remain. The mechanisms of action such as the potential impact on the cellular communication, which would limit its clinical transformation, are still unclear. Based on the above challenges, possible future directions include further optimizing various nanomaterials and elucidating the precise mechanisms between the cell and nanomaterials, to achieve better imaging and therapeutic effects, and accelerate the translation of nanomaterials into clinical practice.

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