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Nanoparticles Used in Theranostics of Cancer

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ABSTRACT:
Worldwide, cancer is the second most common cause of death. Chemotherapy and other traditional cancer treatments have toxicities that affect normal cells in addition to their intended targets, necessitating the development of novel techniques for more effective cell-specific targeting. The use of nanomaterials as chemical biology tools in cancer theranostics has been thoroughly investigated and researched. It demonstrates more applicability in terms of stability, biocompatibility, and enhanced cell permeability, which lead to accurate targeting and lessen the drawbacks of conventional cancer treatments. Gaining multifunctionality and targeting techniques is an interesting possibility presented by the nanoplatform. The creation of smart nanomaterials, in particular, with the introduction of nanotechnology, has revolutionized the diagnosis and treatment of cancer.It is essential in serving as a link between nanomedicine and the science and technology of various nanoparticles (NPs). NPs in the size range of 1–100 nm are generally regarded as suitable for use in cancer treatments. NPs have the potential to improve the solubility and consistency of therapeutic medicines, enabling site-specific targeting, controlled release, and organ safety. Pathophysiological characteristics, improved permeability and retention (EPR) effects, and a benefit in cancer targeting are all advantages of NPs. Additionally, theranostic nanoparticles have been developed with the integration of therapy and diagnostics into a single system, which may offer more individualized treatment with ideal dosages and the use of imaging technologies to track the delivery, targeting, and response to therapy.

Keywords: Nanoparticle, theranostics, nanomedicines, cancer, nanotechnology

I. INTRODUCTION

Theranostics platform combines two concepts; therapeutic and diagnosis. It uses ability of an imaging agent targeting diseases at molecular level along with which it allows the real-time detection of location of the region affected in the disease, drug monitoring for its distribution and agglomeration as well as visualization of therapeutic outcomes[1 2 5] .Amongst the deadliest diseases, cancer (or malignancy) is convoluted, diverse and horrible disease. This aggressive killer kills millions of people annually and has became a significant global healthcare issue[1 3 4] . Research has focused on developing strategies to combat this life-threatening disease. Therapeutic management of cancer has received significant attention in this setting.Various diagnostic methods have been used to diagnose cancer, including NIR fluorescence and positron emission tomography (PET). Various imaging methods include SPECT, MRI, CT, and photoacoustic imaging (4). Chemotherapy, immunotherapy, gene therapy, photodynamic treatment (PDT), radiation, and hyperthermia are some of the therapeutic options available. Theranostics for cancer combines multiple modalities into a single platform[6] .

Nanotechnology has made significant contributions to cancer therapy and offers a new approach to addressing challenges with traditional chemotherapeutic drugs[7] . It is a painless therapy that promotes human health and can be utilised as a molecular instrument for specialised medical interventions on the molecular level[5] .

Nanotechnology can help diagnose, treat, and manage many malignancies[8] [9] . Nanotechnology can help diagnose and treat cancer. Nanoparticle-based imaging and therapy are under continual investigation. Nanotechnology enables accurate diagnosis, drug administration, and monitoring of therapeutic outcomes. It is expected to play a significant role in personalised medicine and treatments. Nano-formulations such as polymeric nanoparticles, metallic nanoparticles, liposomes, dendrimers, carbon nanotubes, and quantum dots are employed for cancer theranostics purposes [10-17] . Nanoconstructs are a promising cancer therapeutic method that combine nanoparticles (NPs) with ligands. They use a simple design, geometry, and stability can be

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supplied both actively and passively. Nanoconstructs offer advantages over traditional cancer treatments, including reduced toxicity and biodistribution. Their shortcomings include biocompatibility, uneven dispersion, toxicity, and lack of precision.

According to WHO, cancer is the biggest cause of death globally, accounting for approximately ten million deaths in 2020. The most frequent cancers are breast, lung, colon, rectal, and prostate cancer. Tobacco use, a high BMI, alcohol consumption, a low diet of fruits and vegetables, and a lack of physical activity account for almost one-third of cancer fatalities. Cancer-causing infections, such as human papillomavirus (HPV) and hepatitis, account for over 30% of cancer cases in low- and lower-middle-income nations. Many tumours are curable if diagnosed early and treated properly.

Cancer occurs when a small number of cells proliferate uncontrollably and spread throughout the body. DNA damage, a primary cause of cancer, disrupts several regulatorymechanisms. Mechanisms that lead to certain malignant illnesses[18] .

Mutation or changes in genes which are defective in following, cytochrome P450, S-transferase, RAD51C, RAD51D, malignant ovarian epithelial, one-carbon metabolism genes and many more plays crucial role in enhancement of cancer[19] .Cancer development is influenced by tumour heterogeneity, the tumour microenvironment, cancer stem cells (CSCs), and epigenetics which arelater followed by progression of chemotherapeutic resistance and recurrence associated with the same[5] [20]. Chemotherapy may not provide a targeted and effective treatment for patients with metastatic cancer[20]. Immunotherapeutic medications have demonstrated remarkable progress in treating cancer at the primary stage while also preventing metastases and lowering the risk of recurrence [5] [21]. Immunotherapy for cancer comes in a variety of forms, including immune checkpoint inhibitors, T-cell transfer therapy, and monoclonal vaccinations as well as antibodies. Cancer can grow because immunological checkpoints like PD-L1 and CLTA-4 interact with other tumour cell proteins and the immune system. Therefore, a variety of checkpoint inhibitors are employed, including chimeric antigen receptor-mediated nanomedicines that target T cells and PLGA-ICG-R837 for anti-CTLA4 [22]. However, the primary side effect of immune treatment is autoimmune issues. Additionally, research indicates that immune treatment is not as effective against tumour cells as lymphoma [23].

NANO PARTICLES

Materials of a nanorange size, or typically 1–100 nm, are used in medical nanotechnology. These materials are used in the creation and production of medicinal medications and equipment[24] [26].Nanomaterials are distinct from conventional macromolecules due to their numerous special optical, magnetic, and electrical properties that arise as size decreases to the nanoscale. High surface-to-volume ratios, improved electrical conductivity, superparamagnetic behaviour, spectral shift of optical absorption, and distinctive fluorescence properties are some of the common traits shared by typical nanomaterials. Nanomaterials can be used in medicine for controlled release and drug transfer. Increased permeability enabling crossing through biological barriers and improved biocompatibility are also noticeable features[25] [26]. Additionally, there is a high likelihood that these nanoparticles will interact with enzymes, antibodies, and receptors within cells. The ability to modify nanoparticles makes them perfect for precise diagnosis and therapy [27] [28] . The formulations of many theranostic nanoparticle agents are presented in the literature. Nanoparticles are composed of several elements, such as silica, carbon, gold ions, and so forth[29] [30] . They were examined in numerous animal modules and revealed potential uses for a number of imaging probes in the early identification of cancer. Nonetheless, they have disadvantages such as immunogenicity, toxicity, and a sluggish rate of bodily elimination[31] [32]. Polylactic acid (PLA), poly(ε-caprolactone), poly(lactide-co-glycolide) (PLGA), poly(alkylcyanoacrylate), and polyglycolic acid are the most significant molecules used for such systems. Polylactic acid (PLA), poly(ε-caprolactone), poly(lactide-co-glycolide) (PLGA), poly(alkylcyanoacrylate), and polyglycolic acid are the most significant molecules used for such systems. In contrast, peptides, proteins, nucleic acids, dextran ester, and chitosan are examples of natural polymers that are employed.

Naturally, these compounds are great, but because of their interactions with medication molecules, they have short half-lives, non-specific distribution rates, and limited applicability. As a result, artificial, Biodegradable, polymeric nanoparticles were investigated[33] [34] .These polymeric nanoparticles were painstakingly created using synthetic chemistry and modelling research.

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Poly(2-hydroxyethyl-L-aspartamide), poly(L-aspartate), poly(D,L-lactic acid-co-glycolic acid), poly(ε-caprolactone), poly(ethylene glycol) (PEG), poly(N-vinyl pyrrolidone) (PVP), poly(N-isopropyl acrylamide) (PNIPAM), poly (hydroxypropylmethacrylamide) (PHPMA), poly(methyl methacrylate), poly(ethylene glycol), poly-(chloromethyl-styrene) (PCMS), and other synthetic biodegradable polymeric nanocarriers used in anticancer therapy. The various kinds of polymeric nanoparticles for medication delivery are as follows figure 1.

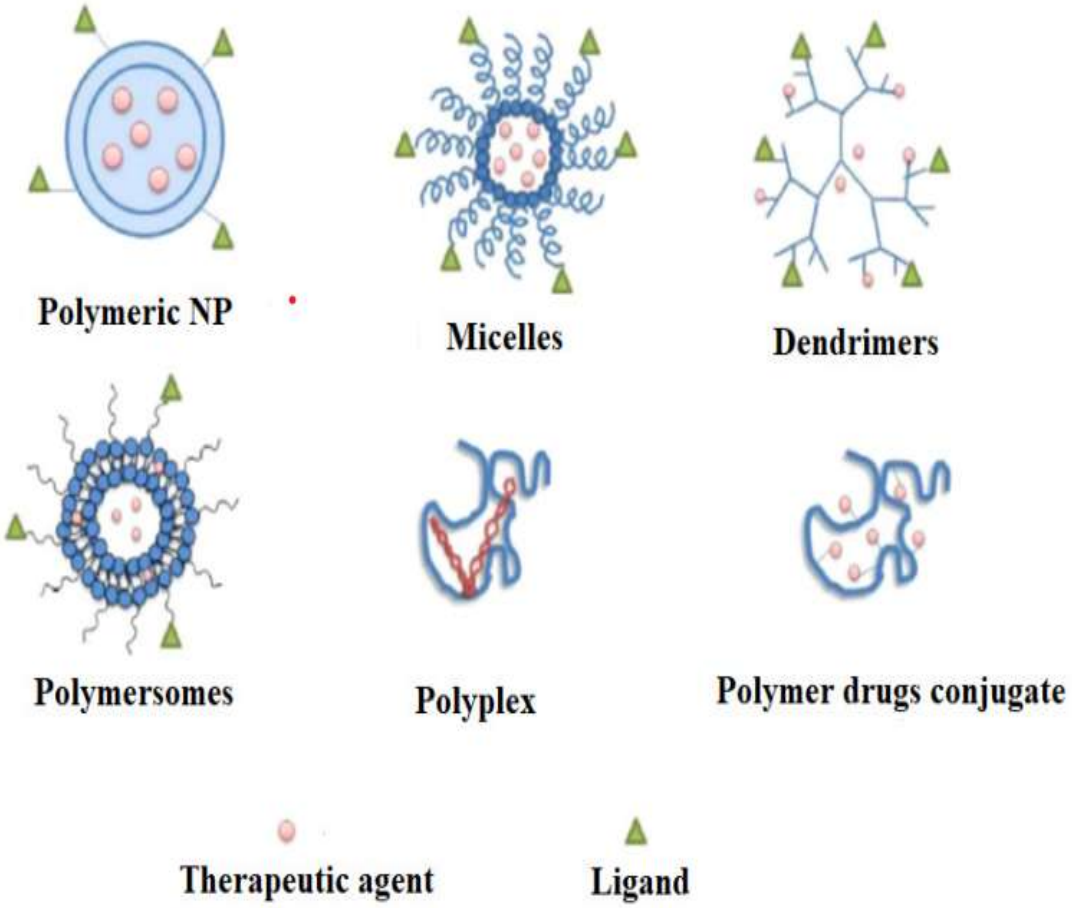

Figure 1: The different kinds of polymeric nanoparticles for drug delivery

Building blocks for nanoconstructs in cancer :

Particles with a diameter of less than 1,000 nm and unique properties that are frequently lacking from larger samples of comparable material types are referred to as nanoparticles (NPs). These can all be classified as 0D, 1D, 2D, or 3D based on the overall form of the nanoparticle[35] . The main parts of NPs are the layers of surface, shell, and core[36] . Apart from nanoconstructs based on organic materials, researchers have also investigated the possibilities of inorganic nanoconstructs based on nonmetallic materials such as iron oxide, gold, and silver.

therapeutic advantages. Black phosphorus (BP) is one of them that has gained a lot of popularity in two-dimensional nanomaterials due to its unique properties and structure. Its unique qualities—such as its biocompatibility and its thermal, optical, electrical, and drug-loading properties—have made it more in demand than 2D nanomaterials that incorporate graphene[5] .

The BP nanomaterials' puckered honeycomb structure, in which every phosphorus atom is sp3 hybridised with a tetrahedral configuration, allows them to demonstrate remarkable optoelectronic, thermal, and mechanical aptitude. Because of this, they can function as photothermal agents, which turn near-infrared energy into heat and so promote photothermal ablation of tumours. Furthermore, reactive oxygen species (ROS), which are essential for the photodynamic treatment of tumours, can be formed

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in ambient oxygen by the energy generated by the excitation of BP NPs. In addition to the elements indicated above that are used in the creation of nanoconstructs, additional organic, inorganic, and hybrid NPs are frequently used in the synthesis of nanostructures.

Table 1: different types of building blocks for nanoconstructs

Carrier system	Material	Drug	ligand	Indication	Reference
Polymeric nanoparticle	PLGA	Temozolomide	Cetuximab	For treatment of EGFR overexpressing cancers	37
	PLGA	ETP	LF	Enhanced anticancer activity in glioblastoma cells	38
	PLGA	Docetaxel	Transferin	Enhanced target selectivity and reduced toxicity in breast cancer cells	39
	PLGA	DTX	Anti-EGFR antibody	Improved cytotoxicity and site specificity in non-small cell lung cancer	40
Bovine Nanoparticles	BSA	Rg5	FA	Breast cancer Therapy	41
	BSA	Paclitaxel	HA	Ovarian cancer therapy	42
Silica or mesoporous silica nanoparticles	Silica	Paclitaxel	HA	Breast cancer therapy	43
	Mesoporous silica	DOX	HA	Enhanced targeting selectivity in HeLa cells	44
	Mesoporous silica	Zinc complexes	Chitosan-Biotin	Enhanced chemotherapy	45
	Mesoporous silica Nanoparticles	Epirubicinv	GalNAc	Targeted cancer therapy of hepatocellular carcinoma	46
Dendrimer	PAMAM	miRNA	ferritin	Treatment of myeloid leukemia	48
	Selenium	pDNA	FA	Cell specific targeting	47
SLN	Stearic acid	Curcumin	Transferrin	Prostate cancer therapy	49
		DOX	FA	Brain cancer therapy	50
	Stearic acid	DOX	Peptide	Prostate cancer therapy	51
	Diacyl glyceride	Tamoxifen citrate	Transferrin	Breast Cancer Therapy	52

Nanoconstructs in cancer theranosis

A new intervention with potential benefits for doctors and patients is cancer therapy. This device combines targeted delivery with diagnostic capabilities to provide real-time cancer therapy monitoring[5 3].

Inorganic material based nanoconstructs

Black phosphorus' unique properties and structure led to its rapid rise in popularity in two-dimensional nanomaterials.

Heterogeneous doping is utilised to improve these kinds of nanoconstructs' stability. In the realm of biomedicine, BP can be conjugated with a variety of metals, polymers, folic acid, albumin, etc. to produce heterogeneous effects. It is possible to create stimuli-responsive nanoconstructs that provide pH-mediated activation and NIR irradiation in order to provide stimuli-responsive BP-based anticancer therapy[5 4]. The BP system has proven its potential for gene delivery in one such application. Mcl-1 is a

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member of the Bcl-2 group and may be targeted in cancer treatments.

Mcl-1 amplification was also observed in breast cancer cells. To target Mcl-1 transcription, BP nanomaterials coupled with PLL for Cas13a/crRNA delivery were developed. AGS cells were used in in vitro tests that showed a 58.64% reduction in Mcl-1 expression and an inhibition of cell activity[55]. The pH-responsive system has the significant advantage of allowing the delivery system to be altered in accordance with the internal environment among stimuli-responsive systems. Mesoporous silica nanoparticles (MSNs) are one type of innovative pH-responsive drug delivery method in which the drug is bonded to the surface using pH-responsive covalent bonds. These are a particular class of optical nanomaterial doped with lanthanide ions, known as upconversion NPs, that show a broad range of electronic transitions in the 4f electron shell. These NPs have the capacity to upconvert one higher-energy photon from two or more lower-energy photons. Mesoporous silica-coated upconversion NPs are coated with copper ions and metal-phenolic networks of tannic acid to create the nanoconstruct. These methods enable medication release to the target site simultaneously, allowing for real-time monitoring. These systems contain anticancer medications, therefore this nanoparticulate form aids in the effective administration of cancer therapy[56].

Polymer based nanoconstructs

Polymeric nanoconstructs are currently being used for cancer theranosis due to their adaptability to surface modification, reactivity to stimuli, and capacity to contain both lipophilic and hydrophilic bioactives or diagnostic agents. Deformable discoidal nanoconstructs, which are employed as a novel delivery method for imaging and therapeutic applications, are one such example. PEG and PLGA are polymerized into a discoidal form to create these. These polymer matrices contain hydrophilic and hydrophobic microdomains that serve as pockets for different medicinal and imaging agents. Because these particles stay in the circulation for a longer period of time, they slow down the rate at which the Mononuclear Phagocyte System (MPS) sequesters them. Furthermore, these polymeric matrices provide the simple integration of polymer-drug conjugates, lipid-drug conjugates, and contrast agents, resulting in the development of genuine theranosis agents[57].

At the moment, a cutting-edge optical imaging technique called fluorescence resonance energy transfer (FRET) may be utilised to track medication release from NPs at the intended tumour location[58].

Furthermore, the potential of PLGA-based nanoconstructs for radiodynamic therapy was investigated. The generation of ROS at the tumour site is the foundation of this anticancer treatment. It primarily addresses the hypoxia brought on by the tumour, which lowers oxygen levels and produces ROS. In one unique method, verteporfin and perfluorooctylbromide are loaded into PLGA NPs to create nanoconstructs. Under normoxic and hypoxic circumstances, these nanoconstructs exhibit a sharp rise in ROS production. In people, this treatment has eliminated over 60% of pancreatic cancer cells, and in just two weeks, tumour development was stopped. These success rates demonstrate that radiodynamic therapy-based nanoconstructs offer superior, non-invasive treatment for hypoxic tumours positioned deep within the body[59]. Due to their stimuli-responsiveness and biodegradability, other polymeric nanoconstructs, like polyurethanes (PU) nanoconstructs, are frequently employed in biomedical applications class. PU nanoconstructs are easy-to-use medication and cancer delivery methods. These kinds of nanoconstructs have a variety of characteristics, including stimuli sensitivity, targeting, quick drug release, and the solubility of hydrophobic chemotherapeutics. They are able to be actively targeted by conjugating with ligands. They are ideal nanocarriers because they are responsive to temperature, pH, stimulation, and other environmental conditions [60].

Dendrimer based nanoconstructs

PAMAM dendrimers are spherical, highly branched macromolecules that can encapsulate active chemicals and stabilise metal NPs, such gold NPs. A study investigated the possibility of using dendrimer-gold hybrid structures loaded with curcumin for thermogenesis. A dendrimer-gold hybrid structure was created by fusing PEGylated amine-terminated $AuCl_4^-$ ions with generation five poly(amidoamine) dendrimers. The MUC-1 aptamer was coupled with curcumin to create the final hybrid system. In contrast to the nontargeted method, the results demonstrated enhanced cellular cytotoxicity in HT29 and C26 cells and demonstrated potential for use in cancer therapy and CT scan-based tumour imaging[61].

A different study showed how to chemically produce hyperbranched PAMAM dendrimers based on unimolecular micelles and coupled with F3 peptide to target the overexpressed cellular nucleolin in MDA-MB-231 cells. In MDA-

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MB-231 cells, PAMAM micelles with an F3 attachment (PAMAM-DOX-F3) showed improved uptake. The 64Cu was chelated to micelles in order to track their pharmacokinetic behaviour for PET imaging. Compared to 64Cu-PAMAM-DOX, 64Cu-PAMAM-DOX-F3 accumulated in MDA-MB-231 tumours more rapidly, efficiently, and persistently, according to serial PET imaging. Remarkably similar distribution features were found in various organs and tissues[5 6 2].

Miscellaneous nanoconstruct

The number of authorised treatments that combine several treatment modalities or the concurrent ingestion of two or more pharmacological therapeutic substances has steadily increased. Frequently, a drug's strongest molecule might not be sufficient to fully solve the issue.

As a result, administering two or more therapeutic drugs together in modern times may help achieve more intracellular targets and eliminate them more effectively[5] .

In experimental rabbits, fumagillin was given as a single injection of αVβ3 integrin-targeted paramagnetic NPs in combination with oral atorvastatin, resulting in a lasting effect of antiangiogenic activity[6 3]. In a different work, protein-based hybrid nanoparticles (NPs) encapsulating poly (sodium-4-styrenesulfonate)/doxorubicin (DOTX)-modified gold nanorods were created for dual chemotherapy and combination plasmonic-based photothermal treatment (PPTT). NIR light regulated the release of DOX, whereas diffusion led to the release of DTX. Following NIR irradiation, the cytotoxicity results in MDA-MB231 cells showed a synergistic effect between the two medications[6 4] .One of the reports described the development of a polyvalent theranosticnanocarrier consisting of folic acid-polyamidoamine dendrimers (FAPAMAM) on the surface and superparamagnetic iron oxide nanoparticles (SPIONs) on the core. Additionally, a very potent hydrophobic anticancer medication known as 3,4-difluorobenzylidene-curcumin (CDF) was coloaded in the FAPAMAM dendrimer in order to improve its solubility and assess its therapeutic potential. As a result, SPIONs@FA-PAMAM-CDF, which are targeted NPs, exhibit improved anticancer activity against HeLa and SKOV3 cancer cells as well as strong MR contrast[6 5] .

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