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## Review Article

# Novel tumor targeting nanoparticles for targeted cancer therapy

Shinde Nikita\*, Dhomase Rutuja, Thorat Suvarna

Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Kopargaon

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### ABSTRACT

Targeted cancer therapy using tumor-specific nanoparticles represents a groundbreaking approach in modern oncology. By exploiting the unique characteristics of the tumor microenvironment and leveraging advanced nanotechnology, these nanosystems enhance therapeutic efficacy while minimizing off-target toxicity. Tumor-targeting nanoparticles are designed to improve the solubility, stability, and bioavailability of anticancer drugs. They achieve selective tumor accumulation via passive targeting, driven by the enhanced permeability and retention (EPR) effect, and active targeting through functionalized ligands like antibodies, peptides, or aptamers. Recent advancements include the development of stimuli-responsive nanoparticles that release their payload in response to tumor-specific conditions such as acidic pH, hypoxia, or enzymatic activity. These versatile platforms, encompassing liposomes, polymeric nanoparticles, metallic nanostructures, and hybrid systems, also facilitate multimodal applications like theranostics, combining therapy with imaging. Despite significant progress, challenges such as immune clearance, stability, and scalable manufacturing persist. This abstract highlights the potential of tumor-targeting nanoparticles in transforming cancer therapy, offering a paradigm shift towards precision medicine. By integrating nanotechnology with molecular oncology, these innovations hold the promise of revolutionizing cancer treatment, delivering safer and more effective solutions tailored to individual patients.

### INTRODUCTION

Cancer denotes a group of diseases determined by the malignant form of abnormal tissue growth (neoplasm), resulting in cells without a normal morphology and/or function. (1) Cancer is a broad term for a group of diseases marked by

uncontrolled and random cell division and invasiveness. Significant efforts have been made over the years to identify various cancer risk factors. In some cases, the causes of cancer have been significantly linked to specific environmental factors, such as radiation and pollution.

**\*Corresponding Author:** Shinde Nikita

**Address:** Rashtrasant Janardhan Swami College of Pharmacy, Kokamthan, Kopargaon.

**Email** ✉: [Shindenikita1582@gmail.com](mailto:Shindenikita1582@gmail.com)

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Additionally, an unhealthy lifestyle characterized by a poor diet, tobacco use, stress, and lack of exercise greatly influences the risk of developing cancer. (2) A report from the World Health Organization (WHO) identifies cancer as the second leading cause of death globally, with more than 18 million cases and nearly 10 million deaths attributed to cancer in 2018. Given the swift rate of industrialization, cancer mortality rates are expected to nearly double by 2040. (3) Cancer is a major public health issue worldwide and ranks as the second leading cause of death. The American Cancer Society estimates that there will be 1.9 million new cases by the end of 2021. (4) The standard treatment methods for cancer consist of surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, and hormone therapy. (5) While chemotherapy and radiation therapy have the capacity for cytostasis and cytotoxicity. (6) Neoplastic tissues can be categorized into three subcompartments: vascular, interstitial, and cellular. (7)

#### **Novel Tumor Targeting Nanoparticles:**

Tumors are intricate tissues made up of neoplastic cells, and in the case of carcinomas, they include stromal cell compartments that contain various mesenchymal cells, particularly fibroblasts, myofibroblasts, endothelial cells, pericytes, and different immune-related inflammatory cells. (8) The rapid expansion of tumors results in uneven vascularization, inconsistent blood flow, and elevated interstitial fluid pressure, which hinders both convection and diffusion. (9)

#### **Types of Nanoparticles as Drug Delivery Systems.**

Nanoparticles can be made from various materials, including polymers, metals, and ceramics. Depending on their manufacturing techniques and the materials employed, these particles can take on a wide range of shapes and sizes, each with unique properties. Numerous types of nanoparticles are currently in different stages of development as

drug delivery systems, such as liposomes and other lipid-based carriers (including lipid emulsions and lipid-drug complexes), polymer-drug conjugates, polymer microspheres, micelles, and various ligand-targeted products like immunoconjugates. (10)

#### **Multifunctional Nanoparticles for Tumor Imaging**

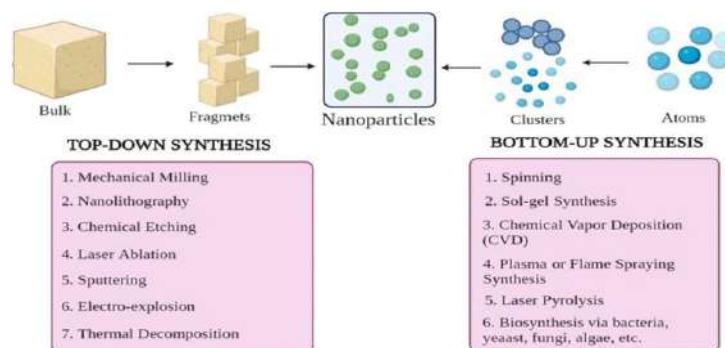
Tumor imaging is essential in clinical oncology, as radiological assessments can identify solid tumors, assess recurrence, and track therapeutic responses. Traditional imaging techniques like CT and MRI primarily focus on the morphological characteristics of tumors, tissues, and organs, detailing aspects such as anatomical location, extent, and size at various levels of spatial resolution and contrast. Despite ongoing advancements in spatial resolution with newer imaging technologies, methods that utilize nontargeted contrast agents like CT and MRI have limitations in sensitivity and in providing specific functional information about the disease. This shortcoming is increasingly recognized as a barrier to earlier diagnosis and effective monitoring of treatment responses. (11)

#### **Nanoparticles:**

Nanoparticles (NPs) are defined as particles that have at least one dimension smaller than 100 nm and exhibit unique properties that are typically absent in bulk materials of the same substance. Based on their overall shape, nanoparticles can be categorized as 0D, 1D, 2D, or 3D (12) Nanoparticles are generally defined as submicronic ( $< 1 \mu\text{m}$ ) colloidal systems, often made from polymers (which may or may not be biodegradable). Depending on the preparation method, nanoparticles can take the form of either nanospheres or nanocapsules. Nanospheres are matrix systems where the drug is distributed throughout the particle, whereas nanocapsules are vesicular systems that contain the drug within an aqueous or oily cavity encased by a single

polymeric membrane. Consequently, nanocapsules can be viewed as a "reservoir" system. (13) The fundamental structure of nanoparticles is quite intricate, consisting of a surface layer, a shell layer, and a core, which is essentially the central part of the nanoparticle and is commonly referred to as the nanoparticle itself. Nanoparticles are known for their ability to penetrate deeply into tissues, which enhances the permeability and retention (EPR) effect. (14)

### Synthesis of NPs



**Figure. 1 Methods of synthesis of nanoparticles**

#### Top-Down Approach

Also referred to as the destructive method, this approach involves breaking down bulk materials to create nanoparticles (NPs). A larger molecule is decomposed into smaller units that are then transformed into NPs. Techniques used in this method include mechanical milling, nanolithography, chemical etching, laser ablation, sputtering, electro-explosion, and thermal decomposition.

#### Bottom-Up Approach

This method focuses on constructing materials from atoms to clusters to nanoparticles (NPs), essentially building them from simpler

Nanoparticles (NPs) come in various shapes, sizes, and structures, achieved through a variety of synthesis methods. These methods can be broadly divided into two main categories:

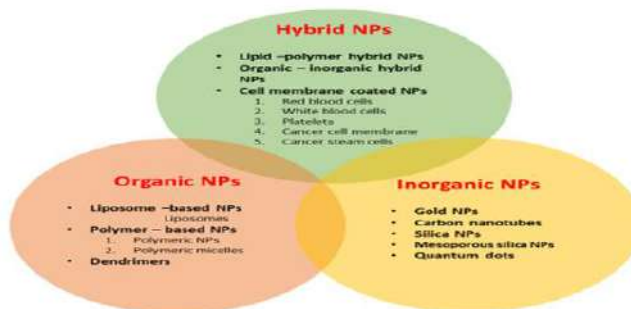
1. Bottom-up approach
2. Top-down approach

Each of these approaches can be further subdivided into different subclasses depending on the reaction conditions and operational techniques used.

substances, which is why it is referred to as the constructive method. Common techniques used in this approach include spinning, sol-gel synthesis, chemical vapor deposition (CVD), plasma or flame spraying synthesis, laser pyrolysis, and biosynthesis.

#### Types of Nanoparticles

Nanoparticles are classified based on their composition, structure, and properties, with major types including organic nanoparticles, inorganic nanoparticles, and hybrid nanoparticles. These types exhibit distinct characteristics, making them suitable for various applications in drug delivery, diagnostics, and therapeutic interventions.



**Figure. 2 Various Types of Nanoparticles (15)**

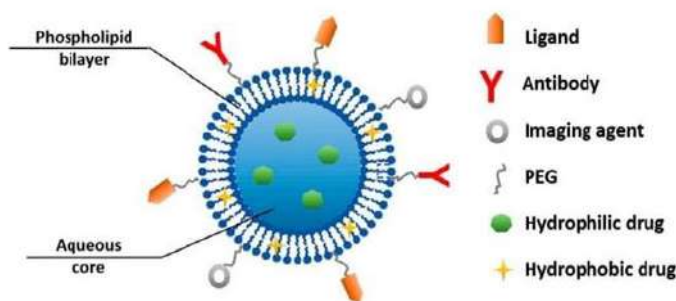
**A) Organic NPs:**

Organic nanoparticles (NPs) have been extensively researched for decades and encompass a variety of materials. The types of organic NPs that have been studied include liposome NPs, polymer NPs, and dendrimers. (16)

**1.Liposomes:**

Liposomes were the first nanoscale drug approved in 1965. (17) Liposomes are among the most extensively studied structures for creating effective drug carriers. Their unique design, featuring an aqueous core surrounded by a phospholipid bilayer, enables them to deliver both

hydrophilic and hydrophobic drugs. Additionally, liposomes possess several advantageous properties, such as biocompatibility, efficient drug encapsulation, size control, and ease of functionalization. However, they are known to have a short circulation half-life, which can be improved through PEGylation. Their capacity for surface modification also allows for the development of multifunctional, liposome-based nanoparticles with enhanced targeting capabilities for tumor sites.

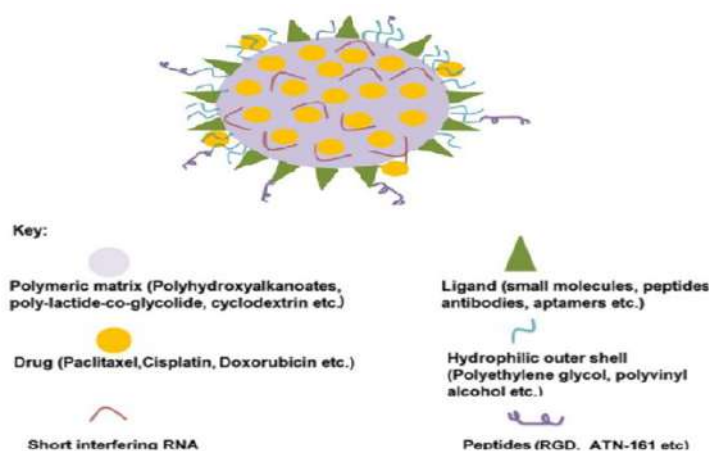


**Figure. 3 Schematic representation of a multifunctional liposome-based nanoparticle.(18)**

**Polymeric Based Nanoparticles:**

Polymeric nanoparticles (PNPs) are colloidal particles that are submicron in size. An anticancer agent of interest can be adsorbed, encapsulated, or conjugated either inside or on the surface of the PNPs. These drug-loaded PNPs form a targeted delivery system designed for the sustained release

of anticancer therapies at specific sites. The polymer shell safeguards the drug from degradation by enzymes in the body. (19)The release of an anticancer agent from the PNPs is governed by diffusion, hydrolysis, enzymatic degradation, or a combination of these processes. (20)



**Figure. 4 A schematic representation of structure of polymeric nanoparticle based targeted drug delivery system. (21)**

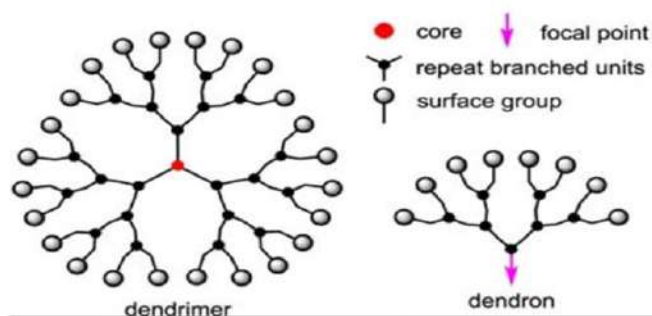
Polymeric micelles are a type of polymeric nanoparticle that feature a hydrophobic core and a hydrophilic shell, formed through the self-assembly of amphiphilic block copolymers in an aqueous solution. The hydrophobic core serves as a solubilization reservoir for poorly water-soluble or hydrophobic agents, enhancing their bioavailability. The hydrophilic shell provides two key benefits: it prolongs circulation time in the bloodstream and improves stability. Tumor-specific ligands can be incorporated into polymeric micelles to boost their accumulation at tumor sites. Consequently, polymeric micelles can play a crucial role in delivering hydrophobic therapeutic agents for cancer treatment. An example includes a polymeric micelle made from PLGA-PEG-retinoic acid (RA) designed for the targeted delivery of irinotecan to HT-29 human colorectal and HepG2 cells. (22)

### 3. Dendrimers

Dendrimers are a distinctive class of highly branched polymeric macromolecules with multiple arms radiating from a central core, creating an almost perfect three-dimensional geometric structure. They can be synthesized using two main strategies:

- a. divergent methods
- b. convergent methods

Divergent methods, introduced by Tomalia in the 1980s, involve the synthesis of three-dimensional polyamidoamine (PAMAM) dendrimers by growing branches that extend radially from a core to the outer edges. These PAMAM dendrimers feature tertiary amines and amide linkages, which enable the binding of various targeting and guest molecules. In contrast, convergent methods begin by synthesizing the dendrimer surfaces by gradually linking together surface unit monomers. Once the surface components reach a sufficient size, several are connected to an appropriate core to form a complete dendrimer. This convergent approach is used to synthesize polypropylene imine (PPI) and polyaryl ether dendrimers. (23) The synthesis of dendrimers begins by reacting an ammonia core with acrylic acid, leading to the formation of a "tri-acid" molecule. This molecule then reacts with ethylenediamine to produce a "tri-amine," which serves as a growth intermediate. This intermediate subsequently reacts with acrylic acid to form a hexa-acid, which in turn produces a "hexa-amine" (Generation 1) product, and this process continues for subsequent generations. Typically, dendrimers range in size from 1 to 10 nm, although they can sometimes reach up to 15 nm. (24)



**Figure.5 schematic structural illustration of dendrimer and a dendron. (25)**

**B) Hybrid Nanoparticles:**

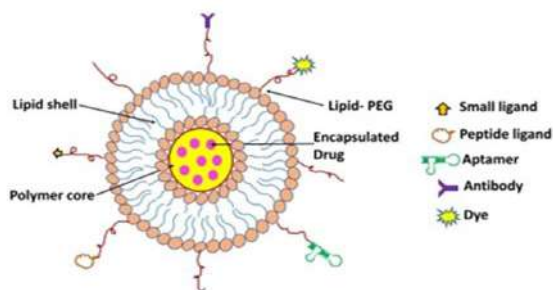
**Lipid –polymer hybrid nanoparticles:**

Lipid-based polymeric nanoparticles (LPHNPs) are highly regarded carrier systems for cancer drug therapy. The assembly of LPHNPs consists of three main components:

1. A polymer core that contains the drug;
2. A lipid monolayer surrounding the polymeric core, which minimizes drug release while protecting the core from water transport;

3. A lipid PEG layer where specific targeting moieties can be attached.

The polymeric core provides excellent structural integrity, storage stability, and controlled release properties, while the lipid and lipid-PEG layers enhance biocompatibility and bioavailability. Overall, LPHNPs are effective, convenient, and reliable carriers for drug delivery.

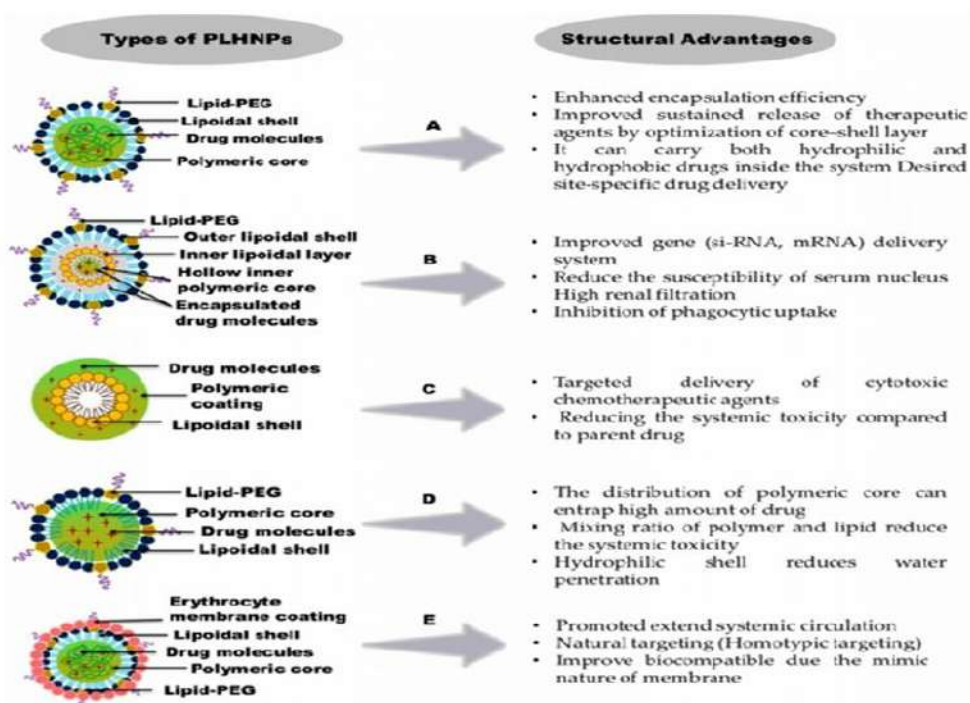


**Figure.6 schematic representation of multifunction LPHNPs comprising structural components and various possible functionalities. (26)**

**Types Of Lphnp.**

LPHNPs can be categorized based on their architecture, which integrates lipid and polymeric structures in the core and shell, respectively. (27) The various types of LPHNPs, along with their structural arrangements, are as follows:

- A) polymer core lipid shell.
- B) core shell-type hollow lipid PLHNPs.
- C) Monolithic PLHNPs
- D) polymer- caged liposome.
- E) Erythrocyte membrane coated PLHNPs.



**Figure.7 Different types of polymer- lipid hybrid nanoparticles and their structural advantages. (28)**

Several methods have been developed for synthesizing LPHNPs, which can be broadly categorized into two main strategies:

- (1) one-step methods.
- (2) Two-step methods.

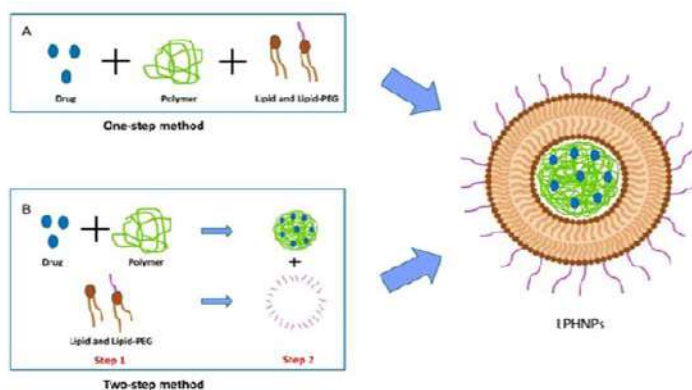
### 1. One-Step Methods

One-step methods primarily utilize the nanoprecipitation technique or emulsification-solvent evaporation techniques. However, nanoprecipitation offers significant advantages over emulsification-solvent evaporation, including

its simplicity and the ability to produce nanoparticles with a narrow size distribution.

### 2. Two-Step Methods

The initial approaches for synthesizing LPHNPs relied on a two-step method, where polymeric nanoparticles are combined with pre-formed liposomes, allowing electrostatic forces to facilitate the attachment of the lipid shell to the polymeric core. The polymeric core can be created using techniques such as nanoprecipitation, emulsification-solvent evaporation, or high-pressure homogenization.

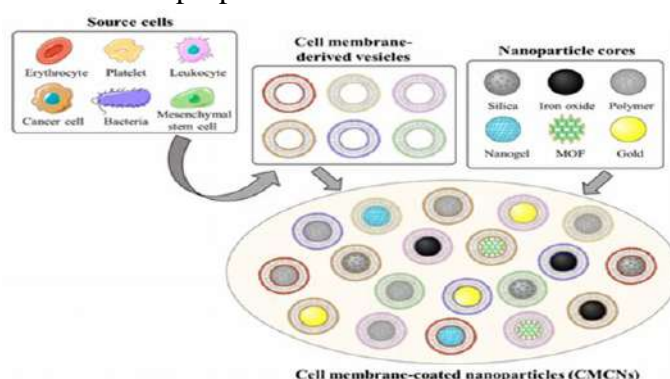


**Figure. 8 Schematic representation of the one-step(A) and two- step(B) methods used for the preparation of LPHNPs.) (29)**

## Cell Membrane Coated Nanoparticles:

### Cell Membrane:

Cell membrane-coated nanoparticles (CMCNs) have been utilized in cancer immunotherapy. They can be employed to deliver immunotherapy drugs and immunomodulators to tumors or directly enhance the effectiveness of cancer immunotherapy through their inherent properties.



**Figure. 9 schematic representation of source and types of CMCNs. (30)**

### 1. Red Blood Cells

Red blood cells (RBCs) are the most numerous cells in the bloodstream, containing haemoglobin, which serves as the primary medium for transporting oxygen. They also play a role in immune function. Due to their circulation time of about 120 days, RBCs make excellent carrier cell membranes for long-lasting drug delivery. They were also the first cell membranes utilized in nanodrug delivery systems. (31) RBC membranes can also target bacteria and absorb pore-forming toxins (PFTs) that are typically released during gram-positive bacterial infections. (32)

### 2. WBC (White Blood Cells)

White blood cells, also known as leukocytes, range in size from 7 to 20  $\mu\text{m}$  in diameter, making them larger than red blood cells. (33)

White Blood Cell Membrane-Coated Nanoparticles: Recent Advances and Medical Applications. (34) White blood cells (WBCs) are typically assessed in standard blood tests and are categorized into five subtypes: basophils, eosinophils, lymphocytes, monocytes, and neutrophils. (35)

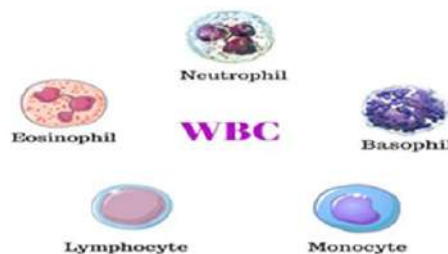
## Preparation of CMCNs:

The preparation of cell membrane-coated nanoparticles (CMCNs) involves three main steps:

1. Isolation and preparation of cell membrane-derived vesicles (CMVs),
2. Synthesis of the nanoparticle cores, and Fusion of the CMVs with the nanoparticle cores.

### 3. Platelets

Platelets originate from the cytoplasmic lysis of mature megakaryocytes. Their plasma membrane is equipped with multifunctional membrane proteins, which are crucial for enabling platelets to fulfil their physiological roles in blood haemostasis. Additionally, the capacity of PMNPs to avoid detection by macrophages is believed to be associated with the CD47 receptor. (36) Approximately 150,000 to 350,000 platelets circulate in each microliter of blood to maintain vascular integrity. Their average lifespan is 8 to 9 days. Platelets are well recognized for their critical role in hemostasis following vascular injury, as well as in wound healing, inflammatory responses, and thrombosis. (37).



**Figure. 10 Various types of WBC**

#### 4. Cancer cell membrane coated nanoparticles:

Cancer cell membranes are an excellent choice for coating nanoparticles in oncological applications. Cancer cells are resilient and can be cultured in large quantities in vitro, facilitating mass collection of their membranes. They also have the unique ability to self-target similar cells (referred to as homotypic targeting), a trait not commonly found in most other membrane sources. (38). Cancer cell membrane (CCM)-coated nanoplateforms are used to create drug delivery systems (DDSs) for the targeted treatment of tumors with homology. (39)

#### 5. Cancer stem cell

Cancer stem cells (CSCs) have been demonstrated to be significantly resistant to standard cancer therapies, including chemotherapy and radiation treatment. (40)

Cancer stem cells (CSCs) are a subset of cells capable of initiating, self-renewing, and maintaining tumor growth. They play a crucial role in tumor metastasis, recurrence, and resistance to cancer therapies.

#### Cancer Stem Cell Biology:

Cancer is characterized by a biological condition in which certain cells within a tissue of an organ undergo uncontrolled division and growth. In 1997, Bonnet and Dick discovered that a small subpopulation of these abnormal cells exhibited

distinct properties compared to the bulk tumor cells. After isolating this group, they showed that these leukemia-initiating cells shared characteristics with stem cells, leading to the introduction of the concept of cancer stem cells (CSCs). (41)

#### Cancer stem cells and their markers:

One of the most promising areas of research in cancer therapy is the targeting of cancer stem cells (CSCs). Evidence suggests that the growth and spread of cancer rely on this small subset of cells known as cancer stem cells. (42)

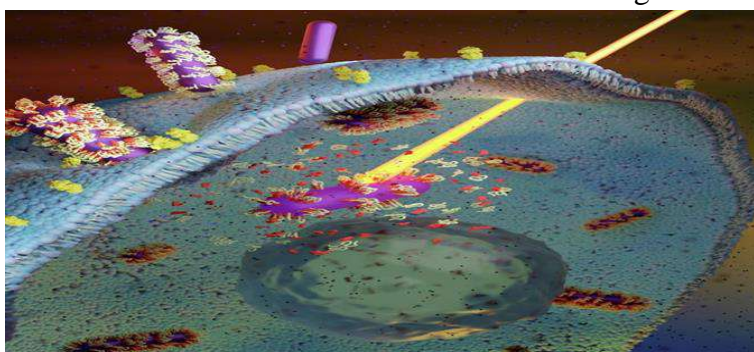
Stem cells exhibit a greater capacity for proliferation, a longer lifespan compared to their progeny, and an increased likelihood of undergoing mutations. (43), (44)

Cancer stem cells (CSCs) are known to be significantly resistant to standard cancer treatments like chemotherapy and radiation therapy. (45)

#### C) Inorganic nanoparticles:

Inorganic nanoparticles (NPs), with sizes down to a few nanometers and a uniform distribution, are highly appealing as passive or active carriers for tumor targeting. (46)

**A) Gold Nanoparticles:** Gold nanoparticles feature straightforward surface chemistry that enables a range of surface modifications, making them suitable for creating biocompatible and functional nano-agents for cancer therapy.



**Figure. 11 schematic representation of gold nanoparticles (47)**

The effectiveness of AuNPs is significantly influenced by their inherent toxicity, so it is essential to examine their toxicological profiles

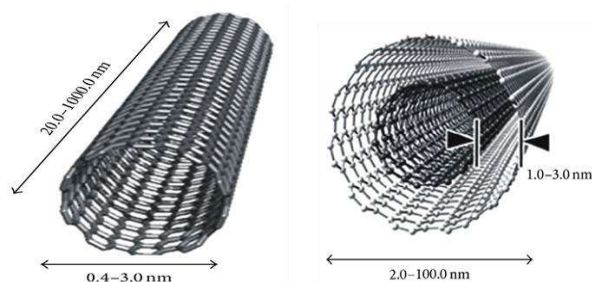
before considering their use in cancer management. (48)

1. Antibody-Directed Gold Nanoparticles:

1. IgG antibodies
2. Antibody fragments and nanobodies
2. Protein-Directed Gold Nanoparticles
3. Peptide-Directed Gold Nanoparticles
4. Aptamer-Directed Gold Nanoparticle
5. Carbohydrate-Directed Gold Nanoparticles
6. Small Molecule-Directed Gold Nanoparticles
7. Gold Nanoparticles with Multiple Targeting Modalities (49)

### B) Carbon Nanotubes Nanoparticles:

Carbon nanotubes, first identified by Iijima in 1991, consist of thin sheets of carbon atoms arranged in benzene rings rolled into a seamless tubular shape. This innovative structure is part of the fullerene family, representing the third allotropic form of carbon alongside graphite and diamond (50). Carbon nanotubes are large



**Figure. 12 Single- walled and double walled carbon nanotubes. (53)**

### C) Quantum Dots:

Quantum dots (QDs) are inorganic nanomaterials that possess intrinsic fluorescent, optical, and electronic properties. (54) Quantum dots (QDs) are luminescent semiconductor nanocrystals at the nanoscale. Their distinctive optical characteristics—including high brightness, long-term stability, the ability to detect multiple signals simultaneously, and tunable emission spectra make them attractive candidates for diagnostic and therapeutic applications in oncology. (55) Quantum dots (QDs) serve as nano-carriers for drugs, facilitating targeted drug delivery and enhancing bioavailability in biological applications. Additionally, a QD nano-carrier system has the potential to enable early detection, monitoring, and localized treatment of specific

cylindrical molecules composed of a hexagonal arrangement of  $sp^2$  hybridized carbon atoms, with a C-C distance of approximately 1.4 Å. The walls of carbon nanotubes can consist of one or multiple layers of graphene sheets. When a single sheet is rolled up, it forms single-walled carbon nanotubes (SWCNTs), while rolling up multiple sheets results in multi-walled carbon nanotubes (MWCNTs). (51)

- Carbon nanotubes (CNTs) consist of single or multiple concentric graphene sheets rolled into cylindrical shapes, with diameters ranging from 0.4 to 100 nm, and lengths extending up to several micrometers. CNTs can be categorized into A) single-walled carbon nanotubes (SWCNTs) and B) multi-walled carbon nanotubes (MWCNTs). (52)

disease sites. (56) Quantum dots (QDs) are a category of nanoscale wide bandgap semiconductors primarily composed of metals, lipids, or polymers. Metal QDs have shown therapeutic potential in early tumor imaging and treatment. However, concerns about biological toxicity have led to the creation of various non-functionalized QDs, including carbon QDs (CQDs), graphene QDs (GQDs), black phosphorus QDs (BPQDs), and perovskite quantum dots (PQDs).

### Properties of QDs

QDs are typically semiconductor materials made from binary and ternary alloys derived from groups II-VI, III-V, and IV-VI of the periodic table, with sizes generally ranging from 2 to 20 nm. Their notable advantages include:

(i) good optical stability and relatively long lifetimes,

(ii) the ability to simultaneously excite multiple QDs using a single light source, and

(iii) narrower and tunable emission spectra coupled with broader absorption spectra. (57)

The most frequently used quantum dots (QDs) include cadmium-based QDs, carbon QDs (CQDs), and graphene QDs (GQDs). (58)

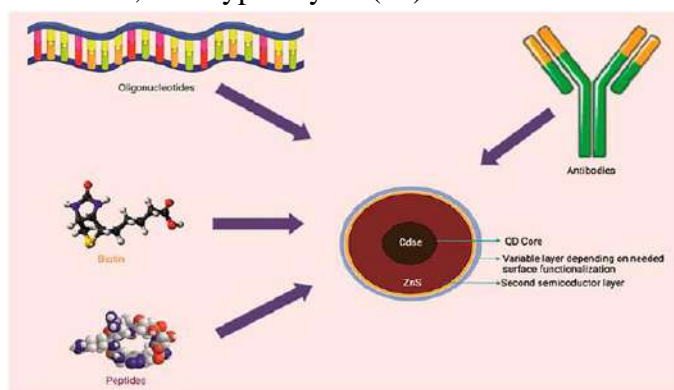
Conventional quantum dots (QDs) consist of a multilayer structure featuring a metallic core material that provides fluorescence. This core is encased in a protective coating that prevents leakage and photobleaching. The most commonly used core materials are cadmium and its derivatives, including cadmium selenide (CdSe) and cadmium sulfide (CdS). These systems have been extensively researched for their stability, size, morphology, photoluminescence, biocompatibility, and toxicity. However, researchers have faced challenges related to low stability, efficacy, and toxicity. (59)

Carbon quantum dots (CQDs), also referred to as carbon dots or carbon nanodots, are typically

smaller than 10 nm and demonstrate enhanced biological properties when compared to traditional semiconductor quantum dots. (60)

These properties encompass high water solubility, strong chemical inertness, ease of processing, and remarkable resistance to photobleaching. The term "carbon dots" was first introduced in 2006 by Sun et al., who chemically synthesized fluorescent carbon nanoparticles using laser ablation of carbon targets followed by surface passivation. (61) Graphene quantum dots (GQDs) are distinct from carbon quantum dots (CQDs) in that they possess an internal graphene lattice, usually measuring less than 100 nm in size and consisting of fewer than ten layers. (62)

The photoluminescence mechanism of graphene quantum dots (GQDs) is mainly affected by edge states, quantum confinement, and surface states. Unlike semi-metallic graphene, GQDs exhibit a non-zero bandgap, allowing them to function as either semiconductors or insulators. The introduction of this bandgap in GQDs improves light absorption and raises the energy spectrum. (63)



**Figure. 13 Schematic representation of simple Quantum dot assembly (64)**

#### D) Silica nanoparticles

Mesoporous silica nanoparticles (MSNs) offer unique advantages due to their large surface area, high pore volume, tunable pore size, diverse surface chemistry, and good biocompatibility, making them promising candidates for cancer diagnosis and treatment. MSN-based delivery systems can enhance therapeutic efficacy while

minimizing cytotoxicity to normal tissues. Additionally, the distinctive properties of MSNs make them suitable for delivering both soluble and insoluble anticancer drugs. (65) The synthesis of monodispersed silica particles utilizes a sol-gel method, first described by Stöber et al. in 1968. This method involves the hydrolysis of tetraalkyl silicates in a solution of alcohol and water, using

ammonia as a catalyst, to produce non-porous silica particles. These particles can be engineered to achieve sizes ranging from a few nanometers to several microns. (66) MSNs have been extensively studied for use in combinational chemotherapy, serving as carriers for both phototherapeutics and chemotherapeutics. (67) Fang et al. attached

indocyanine green (ICG) to mesoporous silica-coated gold nanorods (GNR) to create a carrier for 5-fluorouracil (5-FU), aiming to develop a multimodal imaging-guided synergistic therapy. ICG was utilized for fluorescence imaging and photodynamic therapy (PDT), while 5-FU served as the chemotherapeutic agent. (68)

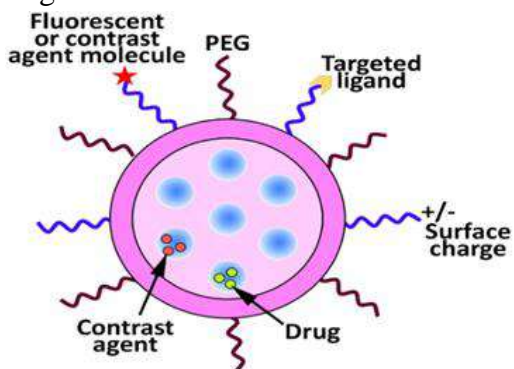


Figure 14. schematic representation of silica nanoparticles. (69)

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