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Review article

Advanced photoluminescent nanomaterials for targeted bioimaging of cancer cells

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ABSTRACT

The investigation of changes in the membrane of cancer cells holds great potential for biomedical applications. Malignant cells exhibit overexpression of receptors, which can be used for targeted drug delivery, therapy, and bioimaging. Targeted bioimaging is one the most accurate imaging methods with a non-invasive nature, allowing for localization of the malignant cell without disrupting cellular integrity. Also, bioimaging has the potential to enhance the quality of established imaging techniques like magnetic resonance imaging (MRI). The utilization of nanoparticles in targeted bioimaging enhances the imaging quality and efficiency. Biocompatible nanoparticles can easily penetrate cell membranes, while they can be readily functionalized on their surfaces toward cell receptors. This study reviews reports on the application of new advanced photoluminescent materials for targeted bioimaging using the cell membrane receptors. Also, the limitations and advantages of the application of nanoparticles have been reviewed along with the clinical consideration of their uses in bioimaging.

Abbreviations:

A549	An epithelial cell line of lung cancer
LPSiNPs	Luminescent porous silicon nanoparticles
AFTN	Afatinib
MCF7	an epithelial cell line of metastatic adenocarcinoma breast tissue
Au	Gold
MIPs	Molecularly imprinted polymers
Ba	Barium
Mn	Manganese
CaCo-2	Colorectal cancer cell line with EGFR receptor
MRI	Magnetic resonance imaging
CAIX	Carbonic anhydrase IX
MSLN	Mesothelin

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CDs/C-dots	carbon dots
MSNs	Mesoporous silica nanoparticles
Cd	Cadmium
MSU-1.1	cell lines of human fibroblast cells
CEA	Carcinoembryonic antigen
MT-MMPs	Membrane-type matrix metalloproteinases
Cet	Cetuximab
N87	Gastric cancer cell line
COS/Dex	Chitosan oligosaccharide/dextran
NCs	Nano clusters
CT scan	Computed tomography scan
NIR	Near infrared
CXCR	Chemokine Receptor
NIS	Sodium/Iodide Symporter
DNA	Deoxyribonucleic acid
NPs	Nanoparticles
DOX	Doxorubicin
NSOM	Near-field scanning optical microscopy
E2	17β-estradiol
PALM	Photo-activated localization microscopy
EGFR	Epidermal growth factor receptor
PAMAM	Polyamide amine
ENG/CD105	Endoglin
PET	Positron emission tomography
Eu	Europium
PLGA NPs	polylactic-coglycolic acid nanoparticles
FAP-alpha	Fibroblast activation protein alpha
PLNPs	Persistent luminescence nanoparticles
FDA	Food and Drug Administration
PSCA	Prostate Stem Cell Antigen
FONs	Fluorescent organic nanoparticles
PTX	Paclitaxel
FR	Folate receptor
QDs	Quantum dots
FRAP	Fluorescence recovery/redistribution after photobleaching
S	Sulfur
FRET	Fluorescence resonance energy transfer
scFv	Single-chain variable fragment
Gd	Gadolinium
Si	Silicon
GFRs	Growth factor receptors
SiNPs	Silicon nanoparticles
GLUT-1	Insulin-independent glucose transporter-1
SPECT	Single photon emission CT
GQDs	Graphene quantum dots
TIRF	Total internal reflection fluorescence
HA	Hyaluronic acid
TNBC	Triple-negative breast tumor cells
HeLa	Cervical cancer cell line
TNFR	Tumor Necrosis Factor Receptor
HER2/ERBB2	Human Epidermal Growth Factor Receptor 2
U87	Glioblastoma cell lines
^{131}I	Iodine
UV	Ultraviolet
ICG	Indocyanine green
VEGF	Vascular endothelial growth factor
IONP	Iron oxide nanoparticles
Zn	zinc

1. Introduction

Cancer is one of the major causes of death worldwide. Although surgery, radiation, and chemotherapy can treat or stop the cancer progress, their systemic effects often harms healthy cells [1]. Consequently, the heterogeneity of tumor cells presents a formidable challenge to systemic treatment. Therefore, gaining a comprehensive understanding of malignant cells is crucial for making breakthroughs in various biological fields. Malignant cells overexpress certain receptors that might be used as targets for therapy [2]. Bioimaging has emerged as an invaluable non-invasive technique for observing biological components and processes [3]. To create a precise and successful diagnostic and therapeutic tool, researchers are focusing on utilizing nanosized particles as fluorescence-based bioimaging and targeted therapy agents. These particles possess exceptional properties, including easy penetration into cells,

biocompatibility, low toxicity, high quantum yield, facile functionalized capabilities, etc. [4]. This method is becoming increasingly popular for studying biological processes at the subcellular and cellular levels, which is helpful to overcome the limitation associated with conventional diagnosis and treatment of cancer cells [3]. This review discusses the application of new materials in the fabrication of bioimaging probes for targeted imaging of cancer cells.

Currently, various medical imaging modalities, including X-ray-based images, magnetic resonance imaging (MRI), ultrasound, and immunohistochemistry, are existed. However, these modalities encounter some limitations such as limited resolution, high cost, time-consuming sample preparation, and providing low information. Table 1 provides a comparison of the most commonly utilized in vivo imaging modalities. Hence, introducing of new imaging probes is essential to enhance the sensitivity, selectivity, resolution, versatility, etc. of the traditional imaging techniques [5]. Cell membrane receptors are proteins that have serve specific functions and play a crucial role in facilitating intercellular communication [6]. Genetic changes alteration within cancer cells can result in the altered production of biological molecules, including cell surface receptors, which can distinguish a healthy cell from a cancerous ones at the molecular level [7]. For instance, estrogen receptors exhibit high amounts in mammary cells, and when 17β-estradiol (E2) binds to these receptors, it triggers intracellular changes that eventually lead to the secretion of growth factors through the endocrine pathway. The expression of Ki67 at the cell surface can induce growth hormone released by other cells to act on Ki67 itself, thereby initiating malignancy through a mechanism. Importantly, Ki67 receptors are absent in healthy mammary cells [8]. Table 2 provides a comprehensive summary of these overexpressed receptors on malignant cells' membranes.

This review article discuss the application of new advanced photoluminescent materials for targeted bioimaging (Scheme 1 and Table 3). The limitations and advantages of the application of nanoparticles have been studied. Furthermore, the clinical consideration of the use new advanced materials in bioimaging were also explored.

2. Nanomaterials for bioimaging

Nanoparticles have gained significant attention in bioimaging due to their enhanced contrast sensitivity, selective binding capabilities, ease of surface modification, and tunable ability to target specific sites, thereby generating detectable signals. Several factors influenced the selection of nanoparticles for bioimaging, including their size, surface area, functionalization potential, improved optical properties, biocompatibility, stability, and versatility across different imaging modalities. In cancer bioimaging, nanoparticles have proven especially effective due to their ability to use the enhanced permeability and retention (EPR) effect, which directs both imaging and therapeutic agents to the tumor site. Additional benefits include targeted imaging, multiplexed detection, improved signal-to-noise ratio, and prolonged circulation time, enhancing diagnostic accuracy [5].

However, designing nanoparticles for bioimaging necessitates careful consideration of several key factors. These include ensuring minimal non-specific binding and uptake, selective binding to cell surface receptors, efficient clearance from the body, and maintaining low toxicity. The long-term fate of nanoparticles within biological systems also plays a critical role in their suitability as contrast agents in diagnostic imaging [9].

The primary challenge in the field of bioimaging revolves around the intrinsic physical characteristics of cancerous cells. Cancer cells pose significant hurdles to effective imaging techniques. Some factors such as the near-infrared (NIR) absorption of cells and the strong absorption of visible light by hemoglobin hinder the penetration of light, are limiting the quality of imaging results. Moreover, scattering, disparate X-ray absorption coefficients between soft and hard tissues, and varying imaging depths are other challenges faced in bioimaging. Utilizing of nanomaterials enhance the contrast, permeability, and retention effect in bioimaging applications [5, 10,11]. Recently, nanomaterials-based probes have become the focus of attention to improve imaging techniques, including positron emission tomography (PET), magnetic resonance imaging (MRI), and optical imaging. Among the different types of nanoparticles, iron oxide nanoparticles have been widely used in MRI, while radioactive metal-free particles have been utilized as radioisotope chelators in PET scanning, and persistent luminescence nanoparticles (PLNPs) in long-lasting NIR luminescence [12]. The use of nanomaterials in biomedical applications offers numerous advantages due to their small size, adjustable biocompatibility, loadable surfaces, and unique chemical features. Furthermore, nanomaterials offer the advantage of loadable surfaces which can be functionalized with specific ligands or targeting agents to improve tumor-specific imaging. This targeted approach enables precise localization of cancer cells or tumors within the body.

2.1. Limitations and cares of application of nanomaterials in bioimaging

Despite the various advantages of nanomaterials, there exist notable limitations hindering their widespread clinical applications. These limitations encompass concerns regarding biodegradability, the potential toxicity arising from degradation during production processes, as well as the toxic structural characteristics exhibited by certain nanomaterials. The immunological reactivity of nanoparticles can be exacerbated by the presence of targeting ligands, repeated administrations, and contamination with endotoxins or pyrogens during the synthesis process, all of which increase their immunogenicity. Moreover, the long-term toxicity of nanoparticles, particularly after their metabolism, remains poorly understood. This raises concerns about their safety in clinical applications [13].

Exploring the factors that influence bioimaging efficiency and uptake processes necessitates a significant examination of various parameters associated with nanomaterials. Key considerations in this context include the size, surface charge, and shape of nanomaterials, all of which play pivotal roles in determining their efficacy as bioimaging agents. Understanding the interplay between these parameters is crucial for optimizing bioimaging outcomes and enhancing the utility of nanomaterials in biomedical applications [14]. On the contrary, one potential mechanism to mitigate the toxicity effects of nanomaterials involves renal clearance, which facilitates the removal of these materials from the body. Renal clearance allows for the elimination of substantial heavy metals and other toxic

Table 1
Comparison of commonly used bioimaging techniques [11,15,94].

Technique	Typical NPs label	Signal measured	Resolution	Depth	Sensitivity (M)	Throughput	Cost	Drawbacks
NIR	QDs, Dye dope silica NPs, rare-earth NPs, Carbon NPs, molecules/polymers	Light, particularly in the near-infrared	2–3 mm	<1 cm	10^{-12}	High	Low	Poor depth penetration, need for probe
MRI	Iron oxide NPs, Gadolinium-based agents	Alternation in magnetic field	25–100 μm	No clinical limit	10^{-9}-10^{-6}	Low	High	Low sensitivity, cannot functionalized with more labels
PET	^{18}F,^{11}C,^{15}O,^{13}N,^{64}Cu,^{124}I,^{68}Ga,^{82}Rb, and^{86}Y	Positron from radionuclides	1–2 mm	No clinical limit	10^{-15}	Low	High	Lack anatomical resolution, Detect only radionuclide, requires radioactivity
X-ray and CT	Iodinated NPs, Heavy elements, Gold NPs	X-rays	50–200 μm	No clinical limit	10^{-3}-10^{-6}	Low	High	Poor resolution of soft tissue
Ultrasound	Perfluorocarbon,	Sound	0.2–1 mm	Several cm	10^{-8}	High	Low	Poor image contrast, works poorly in gases phases

Table 2
A summary of cell membrane receptor overexpressed on malignant cells.

Cell Membrane Receptor	Type of Cancers
Human Epidermal Growth Factor Receptor 2 (HER2/ERBB2)	Breast Cancer
	Gastric Cancer
	Ovarian Cancer
	Endometrial Cancer
PD-L1	Breast Cancer
	Gastric Cancer
	Lung Cancer
	Ovarian Cancer
	Colorectal Cancer
	Bladder Cancer
	Prostate Cancer
	Diffuse large B cell lymphoma (DLBCL)
Growth factor receptors (GFRs)	Head and Neck Carcinoma
	Non-Hodgkin Lymphoma
	Ewing Carcinoma
	Hepatocellular
	Renal cell Carcinoma
	Lung Tumor
	Ovarian Cancer
	Colorectal Cancer
	Bladder Cancer
Tumor Necrosis Factor Receptor (TNFR)	Breast Cancer
	Cervical Cancer
	Colon Cancer
	Renal Cancer
Sodium/Iodide Symporter (NIS)	Thyroid Tumors
Carcinoembryonic antigen (CEA)	Colon Cancer
	Rectum Cancer
	Prostate Cancer
	Ovarian Cancer
	Lung Cancer
	Thyroid Cancer
	Liver Cancer
Somatostatin Receptor	Pituitary Adenoma
	Pancreatic Islet Cell Tumor
	Pheochromocytoma
	Paraganglioma
	Medullary Thyroid Cancer
	Small Cell Lung Carcinoma
Prostate Stem Cell Antigen (PSCA)	Prostate Cancer
Mesothelin (MSLN)	Cholangiocarcinoma
	Breast Cancer
	Lung Tumor
	Ovarian Cancer
Fibroblast activation protein alpha (FAP-alpha)	Breast Cancer
Membrane-type matrix metalloproteinases (MT-MMPs)	Brain Tumors
Carbonic anhydrase IX (CAIX)	Colon Cancer
	Rectum Cancer
	Prostate Cancer
	Ovarian Cancer
	Lung Cancer
	Thyroid Cancer
	Liver Cancer
Chemokine Receptor (CXCR)	Breast Cancer
	Lung Tumor
	Ovarian Cancer
	Colon Cancer
	Rectum Cancer
	Prostate Cancer
MUC1	Breast Cancer
Matriptase	Breast Cancer
Endoglin (ENG; also known as CD105)	Breast Cancer
	Melanoma
Folate Receptor	Ovarian Cancer
	Kidney Cancer
	Brain Tumors
	Endometrioma
	Colorectal Cancer

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Table 2 (*continued*)

Cell Membrane Receptor	Type of Cancers
CD44	Pancreatic Cancer Gastric Cancer Prostate Cancer Testicular Cancer Bladder Cancer Head and Neck Tumors Breast Cancer Non-Small Cell Lung Cancer Lymphoma Colon Cancer Breast Cancer Endometriuma Ovarian Cancer Prostate Cancer Gastric Cancer Oral Squamous Cell Carcinoma

constituents by directing them to the mononuclear phagocytic system (MPS). However, it is essential to note that this process may not completely eliminate the potential risks associated with nanomaterial toxicity, especially in cases where significant accumulation occurs within MPS-rich organs. Toxicological evaluations are essential to assess both the selective tissue distribution of targeted nanoparticles and their potential accumulation within organs, which can compromise microcirculation, particularly in the capillary beds of the lungs, leading to inflammation and granuloma formation [13]. However, determining a standard set of toxicity tests remains challenging, as researchers employ varying methods across different laboratories to assess nanoparticle toxicity. Although this inconsistency presents difficulties, the FDA, in collaboration with the National Cancer Institute (NCI), has developed standardized tests aimed at evaluating the toxicity and efficacy of nanoparticles [15]. To evaluate the toxicity of nanoparticles, various tests and clinical considerations must be undertaken when implementing them for imaging purposes. Toxicity assessments can be conducted using animal models through methods such as behavioral observation, body weight measurements, histological analyses, and hematological studies. Additionally, in vitro studies on cell lines can explore cellular toxicity by assessing parameters like cell viability, apoptosis, DNA damage, and organ function [16,17].

One of the critical assessments in evaluating nanoparticle safety is blood compatibility testing, which is essential for meeting FDA regulatory standards and passing preclinical evaluations. These tests are designed to detect acute toxicities that may arise from the interaction of nanoparticles with blood components. Specifically, they assess the impact of nanoparticles on erythrocytes (hemolysis), platelets, leukocytes, coagulation factors (thrombogenicity), and the complement system (anaphylaxis) when nanoparticles are distributed within the systemic circulation. Such evaluations are crucial for ensuring the safe use of nanoparticles in medical applications, particularly in imaging and therapeutic contexts. These efforts are crucial for ensuring the safe development and application of nanoparticle-based technologies in clinical settings.

So, toxicological evaluations require for both the selective tissue distribution of targeted nanoparticles and the accumulation of nanoparticles within an organ leading to microcirculation compromise, particularly in capillary beds of the lungs resulting in inflammation and granuloma formation [13]. However, it is important to say that deciding which sets of toxicity tests are standard is difficult due to using different tests by researchers from lab to lab to confirm or deny the toxicity. Although, the FDA in collaboration with National Cancer Institute (NCI) are developed the standard tests to determine the nanoparticles toxicity and efficacy [15].

The safety evaluation of nanoparticles for imaging purposes involves four key criteria: 1) mass dose, 2) route of administration, 3) frequency of use, and 4) biological, physical, and effective half-lives. In addition to these, several other factors must be considered for imaging probes before they can be considered for clinical application. These include specificity, sensitivity, in vitro and in vivo studies, systemic toxicity, as well as pharmacokinetic and pharmacodynamics profiles [13].

Biodegradability plays a crucial role in evaluating the long-term safety of nanoparticles, especially for in vivo applications. Ideally, nanoparticles should degrade into non-toxic byproducts that can be efficiently eliminated from the body. Biodegradable nanoparticles, such as those made from polymers like PLGA [18], chitosan [19], or liposomes [20], offer favorable options. In contrast, non-biodegradable nanoparticles, such as those based on metals or carbon, often require surface functionalization to reduce retention and enhance clearance. Additionally, coating non-biodegradable nanoparticles with biodegradable materials can further improve their clearance from the body [13,15].

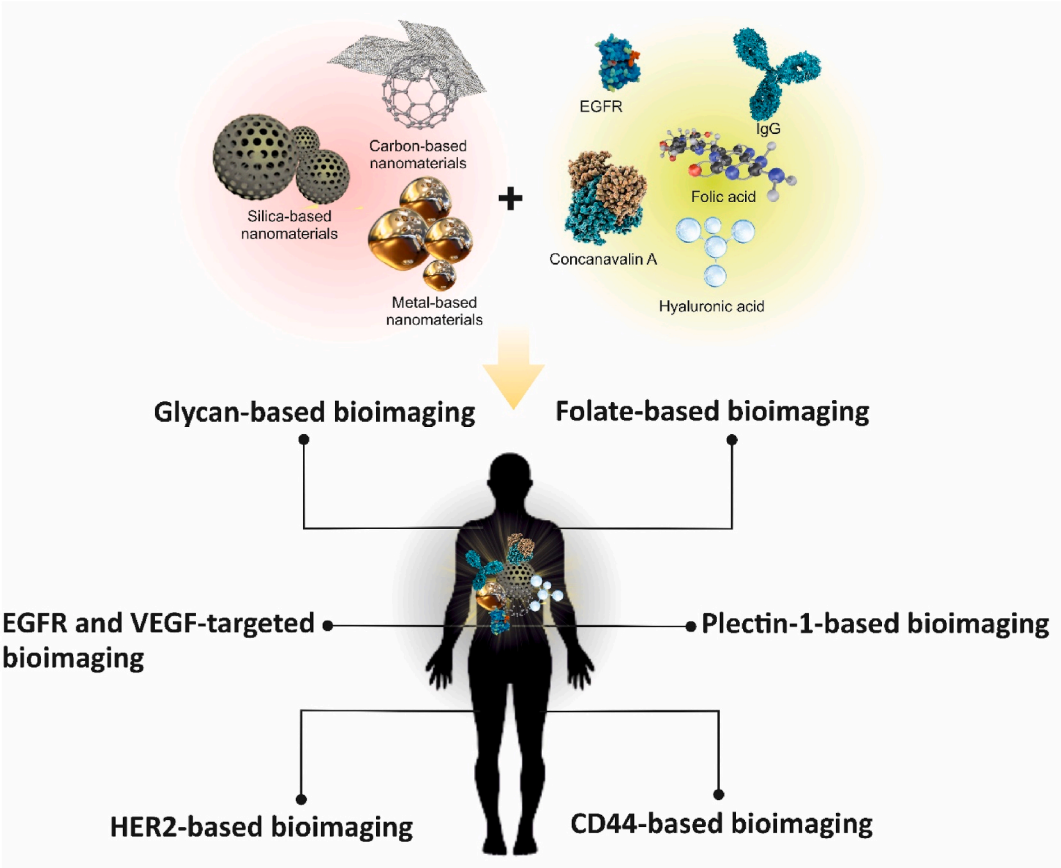
The size of nanoparticles (NPs) emerges as a critical parameter that significantly influences their performance in bioimaging applications. The optimal size of NPs is a subject of ongoing investigation, as it directly impacts key processes such as absorption, dispersion, permeability, and retention within biological systems. NPs of varying sizes exhibit distinct behaviors in terms of their interaction with biological targets, cellular uptake mechanisms, and biodistribution profiles, all of which shape their effectiveness as imaging agents [14]. Furthermore, within the nanomaterials, size emerges as a critical factor influencing the efficacy of targeting cancerous cells in imaging applications. Size exerts a profound impact on various aspects, including biodistribution, blood circulation half-life, cellular uptake, tumor penetration, and targeting specificity [16].

Another consideration pertains to the hydrodynamic size of nanomaterials, particularly in the context of renal clearance. Nanomaterials with a size below 5 nm may exhibit favorable properties for renal clearance; however, their diminutive size could pose

Table 3
A summary of employed materials for targeted bioimaging of malignant cells.

Cell Membrane Receptor	Type of Cancers	Type of Nanomaterials	Merits/Demerits	Ref.
Folate Receptor	Hela Cervical Cancer	TiO2 hybrid nanostructure	Capability to penetrate, NPs shows cytotoxicity after irradiation	[53]
		GQDs	Excellent biocompatibility and negligible cytotoxicity, pH responsive control drug release	[54]
		FA-MnO2/ZnPc nanosheet	High solubility in water, photodynamic therapy	[55]
		SiO2@CDs-FA	Mass production and biological features	[56]
		Gd@CQDs, Eu@CQDs, and Mn@CQDs	Potential for diagnostic and therapeutic purposes	[58]
		Tb2(WO4)3NPs@N-GQDs-FA	Offer a differentiate approach for FR-positive and FR-negative cells	[96]
	Colorectal Cancer	AuNPs/CA/FA	Detecting the signaling of HT 29 cells and improve the specificity of cytosensor towards FR-positive cancer cells	[97]
	Breast Cancer	SiQDs/KCC-NH2@SiO2/FA	Nontoxic, high stability, bright and high quantum yield fluorescence emission	[98]
	Melanoma Cells	Ternary-doped carbon dots	Broad spectrum of multi-color emissions, excellent photostability, biocompatibility, and cellular uptake	[57]
Glycan	HaCaT Cell Line	MIPs nanoparticles	Promising way to detect cancer in early stage	[61]
	N-glycan Receptor	molybdenum disulfide (MoS2) nanosheets attached Aptamer	Capturing DNA	[62]
	Breast Cancer	Au NPs functionalized with mercaptopropionic acid (MPA) and SiQDs	Differentiating glycan receptor-positive cells from negative cells and biocompatible features, high cellular targeting capability	[63]
		AuNPs/Cysteine/FPNPs/Con A NPs	High stability, favorable emission wavelength, and low toxicity	[99]
CD44	Lung Cancer	Chitosan oligosaccharide/dextran	Controllable structure and biological function and high efficient loading of macromolecules	[70]
		HA-Gd-Ce6-PLGA NPs	Show good potential for MR-NIR imaging and photodynamic therapy use	[18]
		Gold-core mesoporous silica-shell nanorods	Induced cell death, promising in theranostics purpose	[73]
	Carcinoma Cancer	MSNs	High cellular uptake with modified NH2 group and HA.	[69]
	Breast Cancer	HA-PEG(SS)-His-Diet-QDs	High efficient in immobilizing Cytochrome C, and entering MCF7 cancer cells	[71]
		MNPs-FPNPs/AuNPs/HA	High specificity toward cancer cells and physicochemical stability	[100]
		Polymeric micelles (FA-HA- FHSV)	deliver paclitaxel (PTX) for bioimaging and targeted therapy in MCF-7	[72]
	Colon Cancer	PFOB@IR825-HA-Cy5.5 nanoprobe	Tumor ablation	[74]
EGFR and VEGF	Lung Cancer	Nanodiamond	Adherence is created by covalent bonds (amide bonds)	[78]
		Nanoprobe by modifying Gadolinium cation and Barium	High affinity toward A549 cells	[80]
	Breast Cancer	Fluorescent organic nanoparticles (FONs)	Covalent attachment and super bright nanoprobe for bioimaging	[79]
		GQDs- scFvB10	pH-dependent release, efficient cell death in unsaturated EGFR cells	[81]
		Nanodiamond	Using MDA-MB-231 cell line lead to more highest target therapy of cytotoxic drug	[82]
		Aptamer-coupled lysosome containing CdSe/ZnS quantum dots	Successful delivery into cytoplasm of the EGFR-positive cells. Lower Bcl-2 expression level and eventual death	[84]
	Colon Cancer	SiNPs	Cytotoxicity above 100 μg/ml	[77]
	Glioblastoma Cancer	Ag-In-S/ZnS quantum dots stabilized on chitosan polysaccharide ligand, and monoclonal antibody.	Bi-functional capabilities combining fluorescent emission for bioimaging and killing activity of cancer cells	[83]
HER2	Breast Cancer	MIP@Silica NPs	Target imaging and therapy with high selectivity	[90]
		Gold Nano-cluster	Photostability under high-intensity UV irradiation/long-time storage.	[89]
	Gastric Cancer	Iron oxide nanoparticles modified with anti-HER2	Strong binding affinity to HER2 receptors on the cells, making excellent contrast agent for photo-acoustic imaging. Low photo-bleaching	[88]

challenges in functionalizing these materials or introducing multivalent target ligands effectively. Achieving a balance between the size requirements for renal clearance and the functionalization of nanomaterials remains a crucial aspect in designing nanomaterials for in vivo applications [21]. Conversely, nanomaterials exceeding 100 nm in size face distinct challenges related to their interaction with the immune system. These larger nanomaterials are readily identified by macrophages and tend to accumulate in organs rich in mononuclear phagocytic systems. Such accumulation can potentially lead to unintended biological responses and impact the overall safety and efficacy of these nanomaterials in clinical settings [16]. Additionally, the utilization of nanomaterials in bioimaging applications necessitates careful consideration of various factors. Primarily, nanomaterials should exhibit dispersibility and stability,



Scheme 1. A graphical representation of the application of materials in targeted bioimaging.

demonstrating resistance to aggregation across diverse in vivo environments while remaining unaffected by factors such as solvent polarity, ionic strength, pH, and temperature. Furthermore, these materials should exhibit minimal non-specific binding, resist uptake by the reticuloendothelial system (RES), and possess low toxicity, particularly regarding reproductive risks, immunetoxicity, and carcinogenic potential, which may manifest over an extended period. It is imperative that these nanomaterials also demonstrate high sensitivity and selectivity towards target cells, providing strong contrast quality in imaging applications. Notably, nanoparticles should enhance large Stokes shifts and exhibit high fluorescence quantum yields in the near-infrared (NIR) spectrum [15,22].

One of the significant challenges in translating nanoparticle-based imaging agents into clinical settings is the economic burden associated with their development. Although these agents hold great potential for future imaging applications due to their ability to facilitate early diagnosis and improve therapeutic effectiveness, the high initial financial investment required for commercialization poses a barrier. Costs related to research and development (R&D), combined with increasingly cautious reimbursement policies from insurers, further complicate this transition. The costs associated with nanoparticle imaging agents vary depending on several items, including their composition, synthesis techniques, surface functionalization, size, batch production, regulatory approval, and intended clinical use. The timeline for developing these imaging agents is typically long and costly. In clinical settings, additional costs arise from the need for high-quality or specialized nanoparticles, advanced equipment, and skilled expertise. Affordable alternatives, such as photoluminescent carbon dots derived from food-waste sources, have been explored to reduce production costs [13].

Therefore, upfront costs, including initial investments in nanoparticle technology, as well as operational costs for maintaining specialized equipment and sourcing reagents, must be considered. However, with future advancements in nanoparticle production and the reduction of associated costs, nanoparticle-based imaging probes have the potential to become a viable alternative to conventional imaging methods like ultrasound, X-ray, and MRI. Hence, the design of nanomaterials for bioimaging modalities requires careful consideration and optimization of the aforementioned parameters.

2.2. Fluorescence-based bioimaging

Fluorescence imaging is a highly sensitive technique that has the capability to detect ligand binding in biosensors, drug delivery, metabolite concentrations, and structural studies [23]. It is preferred to utilize near-infrared wavelengths in the range of 700–750 nm excitation and 750–822 nm emission. For deep tissue imaging, wavelengths in the NIR-IIb range (1500–1700 nm) are desirable,

provided that bright and biocompatible probes are used. However, this approach still faces limitations in imaging depth and is primarily applicable to superficial tumors. Additionally, the number of available luminescent probes within this narrow range is limited, which restricts their application for in vivo imaging [24]. Organic fluorescent dyes, such as Indocyanine green (ICG), can be detected by fluorescence imaging, but they have poor light stability, photobleaching issue, and limited wavelength ranges. These limitations necessitate the development of novel materials that can effectively address these drawbacks. Loading nanoparticles on the surface of the ligand/antibody or encapsulation the particle can improve photoluminescent emission and reduce toxicity. Moreover, these nanoparticles possess additional desirable features such as clinical applicability, photostability, and capability to accurately localize the specific area [25]. By employing functionalized probes, the contrast agents can be optimized, thus enabling real-time visualization of the molecular boundary separating cancerous cells from normal tissue. For example, silver, gold, and copper nanoclusters have their own fluorescence properties that can be utilized in imaging, and their surfaces can be easily coated and protected, further enhancing their potential application [26]. Gold nanoparticles (Au NPs) have a surface Plasmon resonance that can be used in optical imaging techniques such as photoacoustic, magnetic resonance, fluorescence, and X-ray scatter imaging, particularly in the near-infrared region. Furthermore, they exhibit high water solubility and excellent biocompatibility. Silvestri et al. developed Au NPs functionalized with glucosamine that can serve as a contrast agent for CT scans while also providing metabolic information about tissues [27,28]. *In vivo*, studies have shown that these nanoparticles can penetrate tumor tissues effectively [29]. Another important contrast agent used in cancer diagnosis is gadolinium (Gd), which is a paramagnetic agent used as a contrast in MRI. By exposing Gd to Zn^{+2} ions, which are involved in biological reactions, the r1 relaxivity of MRI can be increased. Therefore, Gd can be attached to the targeted molecule to enhance contrast in imaging [30]. Superparamagnetic nanoparticles formed from small crystals of iron oxide can be linked to a variety of particles such as antibodies to function as a contrast or drug carrier, and also for labeling cells [31]. These nanoparticles can be linked to different particles, including antibodies, to enhance their functionality. Additionally, manganese oxide nanoparticles have a short circulation time and offer excellent T1 weighted contrast, with eventual excretion through the liver and urinary system [32]. In the field of cancer diagnosis and bioimaging techniques, Iodine (^{131}I) is a high contrast that can be loaded into tumors. This is particularly useful for emitting gamma rays for single-photon emission computed tomography (SPECT) imaging. To further enhance the effectiveness of this technique, Sun et al. developed a targeted CT/SPECT dual-mode imaging and radionuclide treatment approach using ^{131}I-labeled polyethylenimine functionalized with gold nanoparticles [33]. So, this can greatly improve the accuracy of cancer diagnosis and treatment planning. Ashton et al. aimed to investigate how nanoparticles can enhance different imaging methods. To achieve this, they created three types of nanoparticles: gold nanoparticles coated with ethylene glycol (PEG), nanoparticles that were attached to a full-sized anti-EGFR antibody called cetuximab (C225), and nanoparticles that had a short domain of an anti-EGFR antibody (VHH). These nanoparticles were then subjected to testing on nude mice with A431 subcutaneous tumors and C57BL/6 mice. The findings of the study revealed that the nanoparticles conjugated with cetuximab had a shorter resistance in the bloodstream and a higher accumulation of nanoparticles in the tumor cells. These results demonstrate the potential of nanoparticles in improving the ability to differentiate between benign and malignant tumors [34]. These findings hold great implications for cancer diagnosis and bioimaging techniques.

Bismuth-containing nanoparticles, including bismuth chalcogenides and bismuth oxyhalides, makes them useful for bone regeneration, antibacterial effects, and tumor growth suppression due to their absorbance of X-rays and NIR. One of the key advantages of these nanoparticles is their surface-modifiability with biocompatible proteins and polymers. This surface modification not only enhance their colloidal stability but also reduce their toxicity, making them suitable for biomedical applications [35]. Silicon nanoparticles (SiNPs) have revealed biocompatible and biodegradable, with a high surface area-to-volume ratio, making them useful for bioimaging applications. Luminescent porous silicon nanoparticles (LPSiNPs) can be used for drug delivery and monitoring of accumulation due to their fluorescent properties [21].

Quantum dots (QDs) are semiconducting light-emitting nanoparticles used in molecular imaging, chemical analysis, and biomedical diagnosis. QDs possess several advantages over traditional fluorescent dyes and proteins. One of the key advantages is their

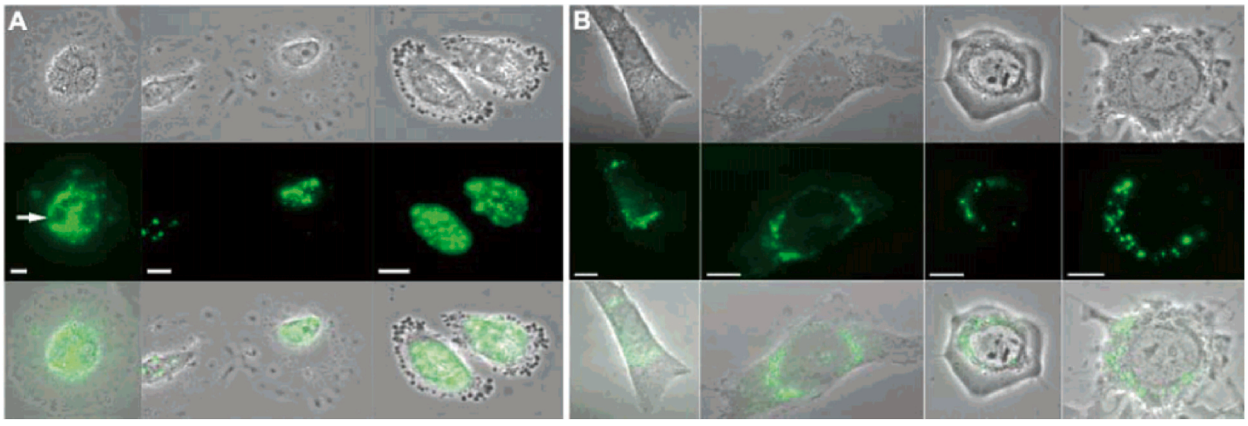


Fig. 1. (A) Attachment of QDs in the nucleus and (B) in the perinuclear region of cells. "Reprinted (adapted) with permission from Ref. [38]. Copyright 2024 American Chemical Society."

tunable emission, which allows them for the generation of fluorescence colors. Additionally, QDs exhibit high photostability and brightness, making them ideal for long-term imaging studies [36]. By attaching a specific ligand, QDs can be functionalized for specific receptor binding and localized targeting of the biomolecule. Furthermore, coating QDs with PEGylated and paramagnetic lipids enhances their contrast in magnetic resonance imaging [37]. This combination of features makes QDs a versatile tool for various applications in cancer diagnosis. For instance, CdSe/ZnS quantum dot have been successfully employed for living cell detection. These QDs accumulate in the cytoplasm, allowing researchers to track cellular processes in real-time [38] (Fig. 1). Graphene, a two-dimensional single-layer nanostructure consist of carbon atoms arranged in a honeycomb lattice, exhibit a wide range of magnetic, electronic, physiochemical, and biological properties. On particular application of graphene is in the form of graphene quantum dots (QQDs), which possess several advantageous characteristic, including high loading capacity, biocompatibility, facile production, and physiological stability [39]. Additionally, carbon dots (C-dots or CDs), which are nano-sized quasi-spherical luminescent particles, are another type of carbon-based nanomaterial. There are different types of carbon-based nanomaterials, such as carbon nitride quantum dots, polymer dots, graphene quantum dots, and carbon dots. These nanomaterials demonstrated highly biocompatible, meaning they can easily interact with living organisms without causing harm. They are stable, soluble in water, and have surfaces that can be modified with various substances like metals, DNA, and proteins. One significant advantage of these dots is their ability to enter cells through a process called endocytosis, and they can be used for single and two-photon excitations to image cells. Furthermore, doped-CDs represent an even smaller particles (less than 10 nm) that contain impurities like boron, sulfur, and nitrogen that improve their electrical and chemical properties [40].

CDs can be synthesized using either bottom-top or top-down mechanisms. Various methods, such as hydro/solvothermal, microwave-assisted, ultrasonic-assisted, thermal combustion, and electrochemical methods are used to create them [40]. Adding impurities to the CD surface can improve imaging, as shown by the enhancement of fluorescence microscopy and MR imaging seen with iron oxide doped CDs [41]. In medical imaging, the utilization of MR imaging is renowned for its ability to yield detailed anatomical information with high spatial resolution, albeit with limitations in sensitivity. To address this inherent trade-off, the integration of contrast agents, such as contrast agents CDs, with MR imaging has emerged as a promising strategy to not only enhance the imaging quality but also to augment the information available concerning cancer cells [42].

One study involved the creation of a multifunctional nanoparticle was developed by a green chitosan (CS)-carbon dot (CD) hybrid nanogel loaded with silibinin, an anticancer drug, which was able to selectively penetrate MCF7 cells (Fig. 2) [19]. Other carbon-based nanomaterials include, carbon nanotubes, nanodiamond, graphite oxide, and graphene oxide are all classified. Carbon nanotubes can function as near-infrared fluorescent nanoparticles and are used in photoacoustic, Raman, and fluorescence imaging. While by utilizing external labels, MR imaging and positron emission tomography (PET) can be achieved [43]. Graphene oxide nanomaterials possess size-tunable photoluminescence, water solubility, and biocompatibility that could enter the cytoplasm of A549 cells with minimal toxicity [44].

The unique properties of magnetic nanoparticles, specifically their ability to selectively enter targeted areas and generate heat through their superparamagnetic character, make them useful in hyperthermia therapy for cancer. Additionally, these nanoparticles can enhance contrast in MR imaging. By combining magnetic and fluorescent properties, multimodal nanoparticles can be developed for various applications including bioimaging, diagnosis, and drug delivery [45]. This versatility opens up robust avenues for research and innovation in the field of cancer treatment. Surface modifications can also be made to tailor the functions of these materials. For

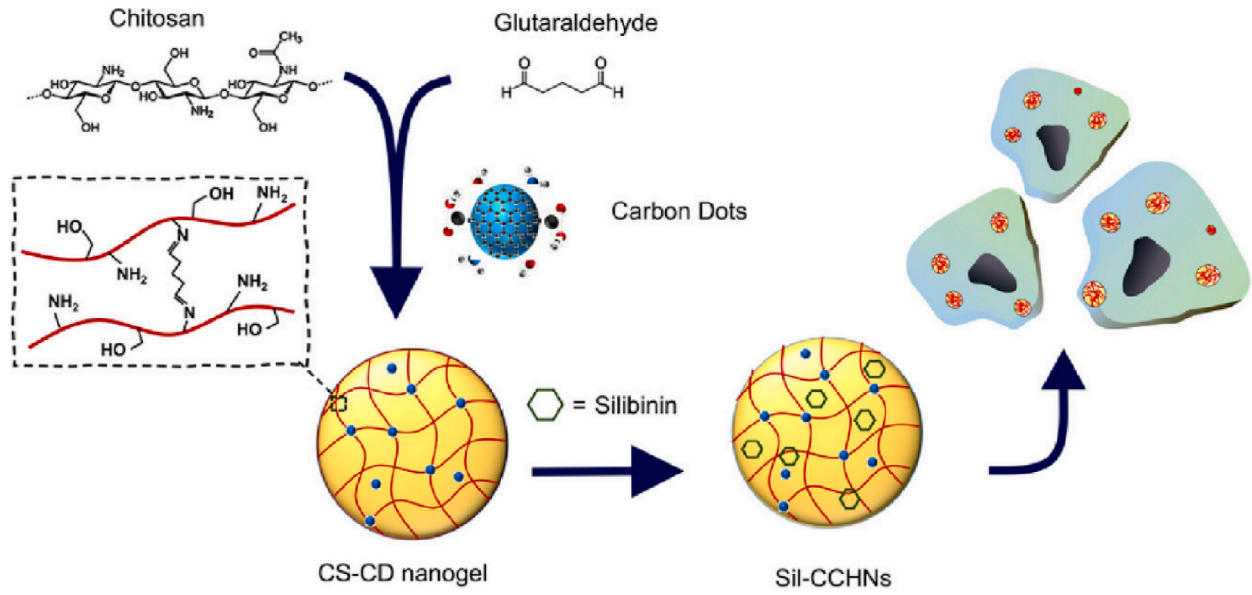


Fig. 2. CS-CD hybrid nanogel loaded with silibinin, an anticancer drug, demonstrating selective penetration into MCF7 cells. "Reprinted from Ref. [19] with permission code of 5878130312616)".

example, Chekina et al. conducted a study where they developed a fluorescent pH-sensitive magnetic nanoprobe by introducing Fluorescein 5-isothiocyanate labeled γ-Fe_2O_3–SiO_2-AP, a silica-coated magnetic nanomaterial that is sensitive to changes in pH [46]. Such surface modifications allow for the customization of these materials to suit specific diagnostic or therapeutic needs.

Hydrogels are three-dimensional networks of hydrophilic polymers that swell in water and have a consistency similar to a solid. They are well-suited for use in tissue environments, as they are non-toxic and biocompatible, and they also exhibit fluorescent properties that make them useful as imaging agents [47]. Polymer dots are fluorescent nanoparticles that have been specifically engineered to target and penetrate cells through endocytosis. They emit bright fluorescence across a wide range, including near-infrared wavelengths. By combining polymer dots with other nanoparticles, it is possible to create multifunctional probes or labeling agents for various applications (Fig. 3) [48]. ICG is commonly used as a diagnostic dye in medicine, but its bleaching limits their wide range uses. Hence, ICG has been incorporated into various nanoparticles to enhance its stability. Recently, ICG has been synthesized as micelles that consist of both ICG and polycaprolactone (PCL). The ICG-PCL micelles have a highly loadable surface and are uniform in size. Fluorescence imaging with these micelles has shown improved brightness, retention time, biocompatibility, and reduced toxicity, as well as greater accumulation of ICG. For instance, camptothecin was loaded onto the surface of the micelles and injected into rats with tumors [49].

3. Targeted bioimaging

3.1. Folate-based bioimaging

Folate is an important substance necessary for DNA synthesis, repair, and cell metabolism which plays a crucial role in various cellular processes. These processes are facilitated by one-carbon metabolism pathways in both the cytosol and mitochondria, which contribute to the synthesis of thymidylate and de novo purine, as well as redox defense and the methionine cycle. Studies have shown increased levels of mitochondrial one-carbon enzymes in cancers [50]. Since highly dividing cells such as tumor cells require more folate, their receptors are overexpressed on the cell surface, especially in malignancies originating from epithelial tissues such as ovarian, breast, and colon cancers [51]. The overexpression of the folate receptor may be associated with poor prognosis [52]. The folate receptor has been a target for cancer treatment for many years, with methotrexate being used as an antifolate agent in hematological cancers [50]. Therefore, the folate receptor can be used as a target for both drug delivery and bioimaging purposes.

Flak et al. used titanium dioxide because of its high UV-light cytotoxicity, biocompatibility, low dark cytotoxicity, and surface properties which make it a suitable option for both diagnosis and therapy (Fig. 4). The proposed hybrid nanostructure containing zinc phthalocyanine, folic acid, and doxorubicin to enhance its diagnostic capabilities. Results from fluorescent imaging indicated that the nanoparticles were able to penetrate HeLa cervical cancer cells more effectively than MSU-1.1 normal fibroblasts. Furthermore, the doxorubicin-loaded nanoparticles exhibited cytotoxicity greater than that resulting from irradiation [53].

In a similar study, Huang et al. conducted a study using graphene quantum dots (GQDs) loaded with doxorubicin and attached to folic acid and gadolinium to create paramagnetic folate GQDs. These nanoparticles were used as a contrast agent for T1-weighted MRI imaging. Tests on zebrafish embryos and HeLa and HepG2 cell lines demonstrated excellent biocompatibility and negligible cytotoxicity. The GQDs were efficiently taken up by HeLa cells with overexpressed folate receptors, as observed through laser scanning confocal microscopy and flow cytometry. The doxorubicin-loaded nanoparticles displayed therapeutic activity through hydrophobic interactions and π–π stacking. The release of doxorubicin varied depending on pH, with 20 % being released at pH 7 and 80 % at pH 5 after 48 h [54]. This pH-responsive release mechanism is advantageous as it allows for controlled drug release in specific acidic tumor microenvironments. The researchers also attached far-red fluorescent dye SQR23 to a liposome membrane through folate receptor embedding, which could have the potential for liposome-based diagnosis and therapy, further expanding their versatility in cancer diagnosis and treatment [20].

Kim et al. proposed a novel scientific hypothesis involving the use of folic acid conjugated manganese dioxide (FA-MnO_2) nanosheets as a carrier for the photosensitizer zinc phthalocyanine (ZnPc) through electrostatic interaction. The nanoparticles (NPs) had

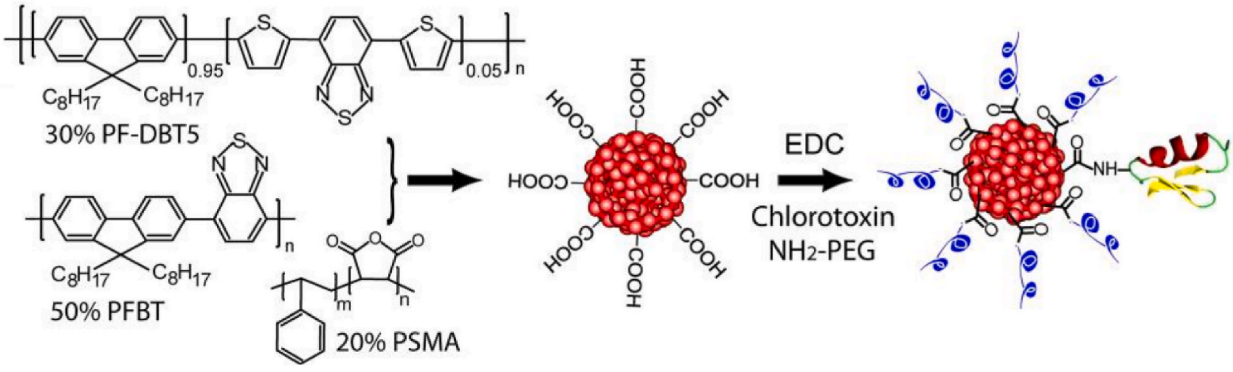


Fig. 3. PB-dot functionalization and CTX conjugation. "Reprinted from Ref. [48] with permission code of 5878140737561)".

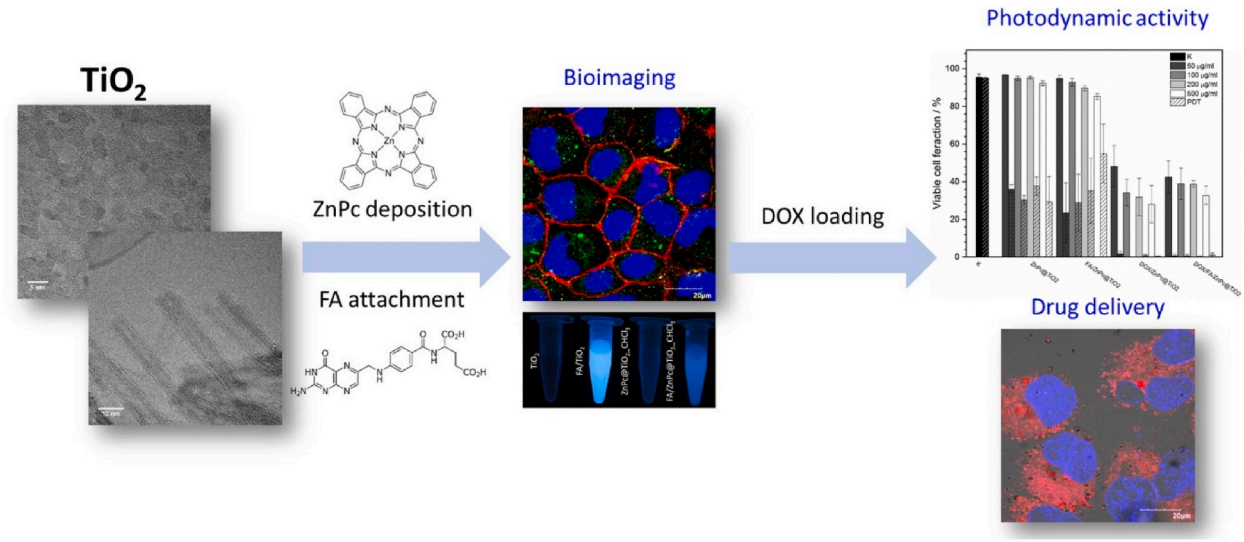


Fig. 4. Schematic representation of application of DOX-loaded TiO_2/zinc phthalocyanine-folic acid for bioimaging and photodynamic therapy. "Reprinted from Ref. [53] with permission code of 5880081084183)".

high solubility in water making them suitable for further investigation. The FA-MnO_2/ZnPc complex exhibited specific attachment to folate-positive cancer cell lines (HeLa) in vitro and in tumor-bearing mice in vivo through folate receptor targeting. In contrast, the MnO_2/ZnPc complex without folate receptor targeting did not exhibit significant fluorescence. Furthermore, ZnPc was released from stimulation by endogenous glutathione, allowing for bioimaging and photodynamic therapy through the generation of singlet oxygen upon light irradiation. This method achieved the desired outcome with only one-tenth of the regular photosensitizer dosage [55].

In addition to Kim et al.'s research, Wang et al. developed silica-loaded carbon dots conjugated with FA (SiO_2@CDs-FA) using a simple one-pot method. The NPs emitted stable blue fluorescence and could be easily separated from the solution, while the SiO_2 spheres acted as carriers. The complex entered folate-positive cells through receptor-mediated endocytosis in HeLa cell lines but not in 293T folate receptor-negative cells. The study highlighted the potential for mass production and biological features of the NPs, which are crucial for their clinical translation [56]. Nasrin et al. synthesized novel ternary-doped carbon dots by hydrothermal process, conjugated to FA. The NPs showed a broad spectrum of multi-color emissions, excellent photostability, biocompatibility, and cellular uptake in folate receptor-positive SKMEL28 melanoma cells. The study suggests the potential for mapping, diagnosing, and photo-therapy for melanoma [57]. Furthermore, Yao et al. designed magnetofluorescent carbon quantum dots using crab shell chitin as the

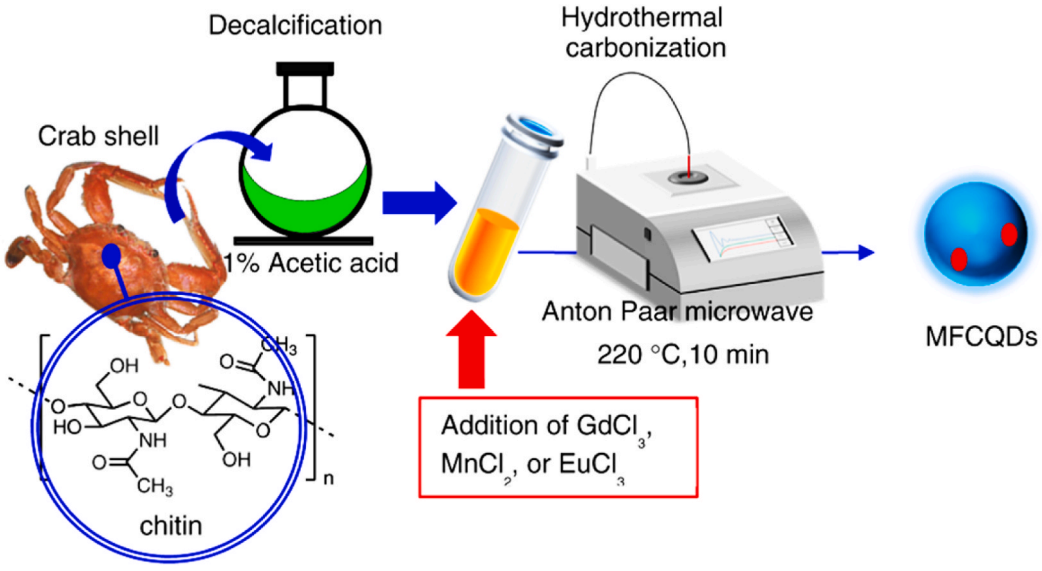


Fig. 5. Schematic representation of the synthesis process for MFCQDs using a microwave-assisted hydrothermal method. "Reprinted (adapted) with permission from Ref. [58]. Copyright 2024 American Chemical Society."

carbon source and added metal ions of Gd^{3+}, Mn^{2+}, and Eu^{3+}. The prepared nanoparticles showed excellent potential for T_1 and T_2 MR imaging contrast. To enhance their specificity towars cancer cells, folic acid conjugation was employed and was loaded doxorubicin onto Gd@CQDs for folate-positive HeLa cells targeted imaging and drug delivery. The results showed that the DOX-loaded nanoparticles had higher cytotoxicity than DOX-free ones, and there was no systemic cytotoxicity in the in vivo study. Gd@CQDs, Eu@CQDs, and Mn@CQDs have the potential for diagnostic and therapeutic purposes (Fig. 5) [58].

In summary, these articles discuss the potential of using folate-targeted nanoparticles for cancer diagnosis and therapy. Folate receptors are overexpressed in highly dividing cells such as tumor cells, making them a good target for drug delivery and bioimaging. Various studies have used different types of nanoparticles, such as titanium dioxide, graphene quantum dots, silica-loaded carbon dots, and magnetofluorescent carbon quantum dots, conjugated with folate and loaded with anticancer drugs like doxorubicin. These nanoparticles have shown efficient cellular uptake and therapeutic activity, as well as potential for diagnostic purposes such as T1-weighted MRI imaging and fluorescence imaging. The studies highlight the biocompatibility and specificity of the nanoparticles for folate receptor-positive cancer cells, suggesting their potential for future clinical applications.

3.2. Glycan-based bioimaging

In cell growth and differentiation, carbohydrate receptors on the cell surface play a crucial role. In cancer cells, hypoxia-induced adaptation leads to increased glycolysis, which raises the demand for glucose and causes overproduction of the insulin-independent glucose transporter-1 (GLUT-1) receptor. This receptor has the potential to be a target for theranostic purposes [59]. Detecting glycosaminoglycan hyaluronic acid (HA) in early-stage cancer through immunohistochemical methods is valuable for diagnosis. However, intracellular HA may be occupied by macromolecules, presenting a challenge. The MIP due to their high selectivity, cost-effective, and reusability nature can be a good candidate for overcome this problem [60]. For instance, Rangel et al. developed fluorescent Molecularly Imprinted Polymers (MIPs) nanoparticles using a solid-phase synthesis method. The MIP NPs were able to attach to the intracellular HA in human keratinocytes (HaCaT cell line), providing a promising solution for early-stage cancer detection [61].

Yao He et al. have developed a responsive electrogenerated chemiluminescence (ECL) bioprobe that specifically targets the N-glycan receptor on the surface of cancer cells. To create this bioprobe, they prepared molybdenum disulfide (MoS_2) nanosheets and attached aptamers and capture DNA to them. They used $Ru(phen)_3^{2+}$ as ECL and concanavalin A (Con A) as a binding protein [62]. Similarly, Jafarzadeh et al. also utilized Con A to connect citrate-stabilized gold nanoparticles functionalized with mercaptopropionic acid (MPA) and silica quantum dots through thiol-AuNPs bonds. These particles were activated using an EDC/NHS reaction. These particles were found and confirmed by flow cytometry and fluorescent imaging that selectively enter MCF-7 breast cancer cells, which are glycan-positive, but not HEK3, which are glycan-negative [63]. Glucose receptors present on the surfaces of liver cell play a crucial role in endocytosis, clearance, and binding of asialoglycoproteins found in the bloodstream. Confocal fluorescent imaging, which has showed a higher uptake and brighter image of galactose-tagged quantum dots in hepatoma cells compared to glycan-negative cells like MCF-7. Unlike galactose, mannose-tagged nanoparticles have shown the ability to enter MCF-7 breast cancer cells, which are known to exhibit high expression of the mannose receptor. Targeting the mannose receptors on immune cells, such as macrophages, could be a possible route for modifying immune cells [64].

As a summary, this discussion has emphasized the importance of carbohydrate receptors on cell surfaces in cell growth and differentiation, with a focus on their role in cancer cells. Among these receotirs, the GLUT-1 receptor is highlighted as a potential target for theranostic purposes in cancer. Various methods of targeting carbohydrate receptors have been described for both cancer detection and treatment. These methods include the use of Molecularly Imprinted Polymers (MIPs) nanoparticles, an electrogenerated chemiluminescence (ECL) bioprobe, as well as gold nanoparticles functionalized with mercaptopropionic acid and silica quantum dots. Different receptors, such as N-glycan and mannose, are also discussed as possible targets for cancer treatment and modifying immune cells. Furthermore, it is important to note that while these findings provide valuable insights into the role of carbohydrate receptors in cancer biology. Future studies should aim to explore additional bioimaging techniques and investigate novel strategies for targeting carbohydrate receptors in order to optimize cancer diagnosis and treatment outcomes.

3.3. CD44-based bioimaging

CD44, a transmembrane glycoprotein, is found on the surface of cells and is produced by a single gene consisting of twenty exons, with the alternative splicing of ten exons leading to the creation of different isoforms of CD44. The protein is made up of extracellular, transmembrane, and intracellular domains, with the extracellular domain being important for binding to hyaluronic acid (HA). The unique structure of CD44 provides a pathway cellular entry, making it a target for bioimaging and drug delivery purposes. Interestingly, high levels of CD44 receptor and HA are found in melanoma tissue, suggesting a role for CD44-HA interaction in cell proliferation and differentiation [65,66].

The overexpression of CD44 is often associated with a poor prognosis and is seen in lymphoma, colon, breast, endometrium, ovarian, prostate, gastric cancers, and oral squamous cell carcinoma [67]. The expression of some variant CD44 (CD44v) is correlated with more metastatic features of the cells. For example, the expression of CD44v6 is related to colorectal cancer with lymph node metastasis [65,68]. A study used mesoporous silica nanoparticles (MSNs) modified with amino groups (MSN-NH_2) and hyaluronic acid (HA) of varying molecular weights to achieve a targeted drug delivery system that can effectively interact with CD44 receptors. The zeta potential test measured an increasing negative value with the increase of the hyaluronic acid chain. Optical and electron microscopy techniques were employed to examine the cellular uptake of HA-free nanoparticles and HA-conjugated nanoparticles in HeLa

cells. It was observed that HA-free nanoparticles entered the cells through an ATP-consuming process known as endocytosis. On the other hand, when the nanoprobe was conjugated with HA, it facilitated penetration into the cell through CD44 receptors on the cell surface. Furthermore, it was found that MSN-NH2 and low-weight HA-conjugated nanoparticles exhibited better cellular uptake compared to larger molecular weights of HA. This highlight the importance of the HA chain length in determining cellular uptake efficiency [69]. Combining chitosan oligosaccharide/dextran (COS/Dex) with hyaluronic acid makes it possible for the nanogel to enter the cells via CD44-mediated endocytosis for targeted therapy purposes. In this study, anionic HA plays the role of a payload for the biomacromolecules in electrostatic-interaction-induced assembly. The introduced nanogel had a controllable structure and biological function (Fig. 6) [70].

Park et al. synthesized nanoparticles using hyaluronic acid, gadolinium ions, NIR photosensitizers (Ce6), and polylactic-coglycolic acid (HA-Gd-Ce6-PLGA NPs), which were able to penetrate CD44-overexpressing A549 cell lines. It could also produce a good contrast on T1-weighted MRI by enabling the chelation of Gd^{3+} due to carboxylate groups of Ha, resulting in a strong contrast on T1-weighted MRI. These nanoparticles showed potential for MR-NIR imaging and photodynamic therapy use, as these nanoparticles caused tumor regression or delay in growth in nanoparticle-treated mice after NIR laser illumination [18]. Furthermore, Fu et al. developed nanoparticles using green-light-emitting quantum dots with redox-sensitive hyaluronic acid ligands (CdZnSeS/ZnS) for intracellular protein drug delivery to CD44 overexpressing MCF7 cell lines. These nanoparticles were efficient in immobilizing Cytochrome C, entering MCF7 breast cancer cells, and releasing intracellular proteins in high concentration off glutathione condition. The HA part of the nanoparticles consists of disulfide-linked polyethylene glycol-histamine- diethylenetriamine (HA-PEG(SS)-His-Diet-QDs). The QD could efficiently immobilize Cytochrome C, enter MCF7 breast cancer cells, and speed up intracellular protein release in high concentration off glutathione condition, which can be a proper nanocarrier for intracellular protein transport with endo/lysosomal escape [71]. Yang et al. designed polymeric micelles using folic acid, hyaluronic acid, and acid-SS-vitamin E succinate (FHSV) to deliver paclitaxel (PTX) for bioimaging and targeted therapy in MCF-7 and NIH3T3 cell lines and S180 tumor-bearing mice. These micelles showed better cellular uptake through CD44 in tumor cells than single receptor-mediated nanoparticles and demonstrated remarkable accumulation and growth inhibition in the tumor while minimizing systemic toxicity in vivo [72]. Furthermore, Jacinto et al. utilized a combination of hyaluronic acid and D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) to enhance the selectivity and biocompatibility of Gold-core mesoporous silica-shell nanorods (AuMSS). This combination resulted in a neutralization of the surface charge in both 1:1 and 4:1 proportions of AuMSS-TPGS-HA formulation. The 4:1 formulation demonstrated improved hemocompatibility and selectivity. The CD44-mediated cellular uptake and photothermal effects induced cell death in HeLa cells, suggesting a promising application for these nanoparticles in theranostics [73].

Liang et al. developed a new PFOB@IR825-HA-Cy5.5 nanoprobe for triple imaging (fluorescent, photoacoustic, and computed tomography) and tumor ablation in Human colon cancer HT-29 cells and mice with HT-29 tumors. This nanoprobe included perfluorooctylbromide, IR825 dye, HA, and Cy5.5 dye, with hyaluronic acid for CD44-mediated uptake and a hyaluronidase-activatable fluorescent dye on the outer surface. The combination of PFOB@IR825-HA-Cy5.5 and NIR laser irradiation resulted in effective tumor ablation in mice, indicating the nanoprobe's safety, efficacy, and potential for theranostic purposes [74] (Fig. 8).

To provide a comprehensive understanding of this hypothesis, it is important to discuss the role of CD44 in cell proliferation and differentiation, as well as its overexpression in various cancers. In summary, CD44 is a glycoprotein found on the surface of cells that has various isoforms created by alternative splicing of its exons. Its involvement in cellular processes makes it an attractive target for cancer research. Several studies have utilized hyaluronic acid as a targeting ligand to deliver drugs or imaging probes to CD44-overexpressing cells, with successful outcomes observed in various in vitro and in vivo experiments. Nanoparticles designed with hyaluronic acid, gadolinium ions, NIR photosensitizers, or quantum dots have shown potential for use in MR-NIR imaging,

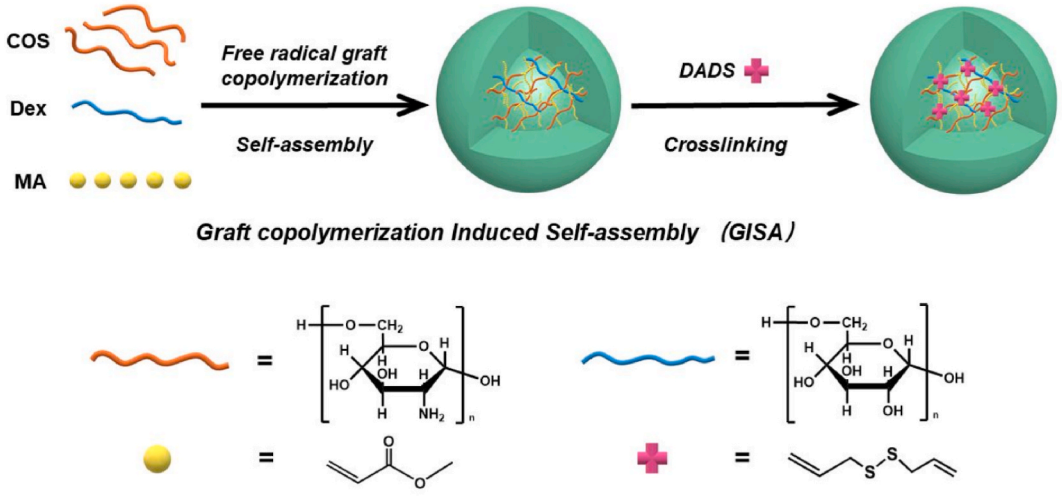


Fig. 6. Schematic representation illustrating the fabrication process of COS/DEx NGs. "Reprinted (adapted) with permission from Ref. [70]. Copyright 2024 American Chemical Society."

photodynamic therapy, or intracellular protein drug delivery. Additionally, combining hyaluronic acid with other materials such as chitosan oligosaccharide/dextran or D-α-tocopherol polyethylene glycol 1000 succinate has resulted in improved selectivity and biocompatibility of nanoparticles for targeted therapy.

3.4. EGFR and VEGF-targeted bioimaging

Epidermal growth factor receptor (EGFR) kinase is associated with angiogenesis, cell proliferation, and metastasis. EGFR is overexpressed in malignancies with epithelial origin such as lung, breast, colon, ovaries, and prostate [75]. Another important player in cancer progression is vascular endothelial growth factor (VEGF), a multifunctional cytokine that stimulates angiogenesis and mediates cell proliferation, invasion, migration, and vascular permeability. The VEGF receptor is highly expressed in several types of cancer, including renal cell carcinoma, non-small-cell lung cancer, hepatocellular carcinoma, glioblastoma, metastatic colorectal, and metastatic breast cancer [76].

Behray et al. synthesized photoluminescence thiourea-functionalized silicon nanoparticles, synthesized by the hydrosilylation reaction mechanism using sulforaphane and allylamine anticancer agents. Confocal microscopy images and flow cytometry demonstrated that the SiNPs had successfully accumulated in EGFR positive colorectal (CaCo-2) cancer cells rather than normal colon epithelial cells. They could actively target the ligand and exploit the EGFR receptor. Cytotoxicity was observed in a dose-dependent manner at concentrations above 100 μg/ml (Fig. 7). The study presents an opportunity for further investigation into the use of receptor-exploiting nanoparticles as anticancer agents [77].

Li et al. used the modified nanodiamond with EGF (ND-EGF) and confocal Raman microscopy to specifically target the EGF receptor on HeLa cells. The bioconjugation of nanodiamond and EGF did not significantly change the zeta potential of the particle, indicating the adherence was primarily through covalent bonds via amide bonds rather than electrostatic ones. Furthermore, the study showed a dose-dependent interaction between nanoparticles and cells, with ND-EGF affecting cell morphology and promoting migration. The technique shows promise as a nanoparticle for bioimaging and therapeutic applications [78]. Aucon et al. designed red-emitting fluorescent organic nanoparticles (FONs) that are non-cytotoxic, biodegradable, and provide good imaging contrast. To target EGFR-overexpressing MDA-MB-468 malignant breast cells, these FONs were conjugated with EGF. The results of this study revealed covalent attachment between FONs and EGF, with EGF-conjugated FONs attaching to EGF receptors in an asymmetric pattern on the cell membrane. The multivalency of EGF (4.7 EGF for each FON) can potentially lead to effective and systematic activation and phosphorylation (EGFR). Additionally, the large diameter of EGF-conjugated FONs could prevent the immediate engulfment of the receptor, providing a bright and localized area in 30 min. Based on these observations, Aucon et al. propose the use of EGF-conjugated FONs as a super bright nanoprobe for bioimaging purposes in cancer diagnosis [79].

Feng et al. designed a nanoprobe by modifying Gadolinium cation and Barium with EGF-based peptides through Gd-phosphonate coordinate bond formation. The researchers then tested the efficacy of this nanoprobe on the A549 pulmonary carcinoma cell line. Remarkably, they found that the nanoparticles accumulated inside the A549 cells with a high affinity. Moreover, to evaluate its

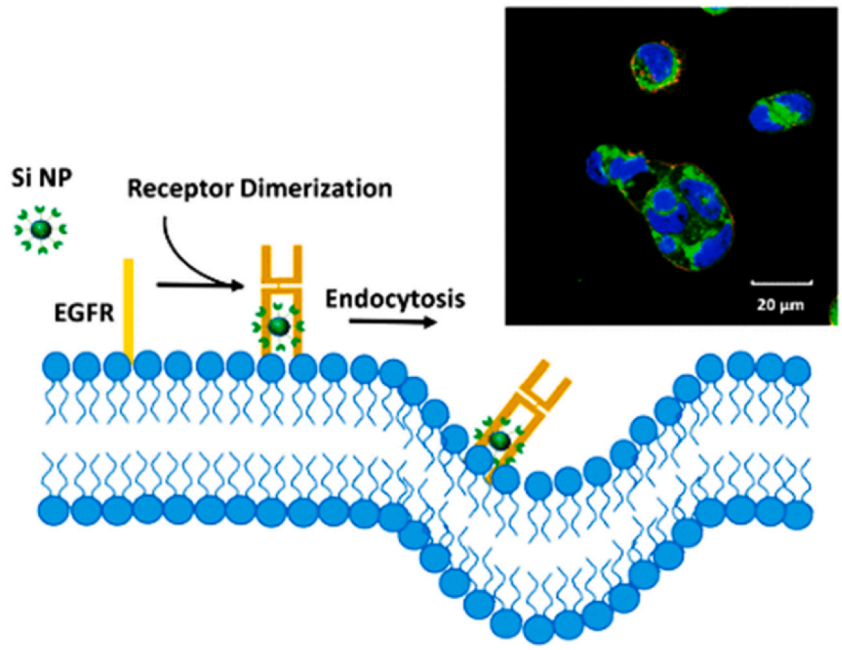


Fig. 7. Successful accumulation of SiNPs in EGFR-positive colorectal (CaCo-2) cancer cells compared to normal colon epithelial cells. "Reprinted (adapted) with permission from Ref. [77]. Copyright 2024 American Chemical Society."

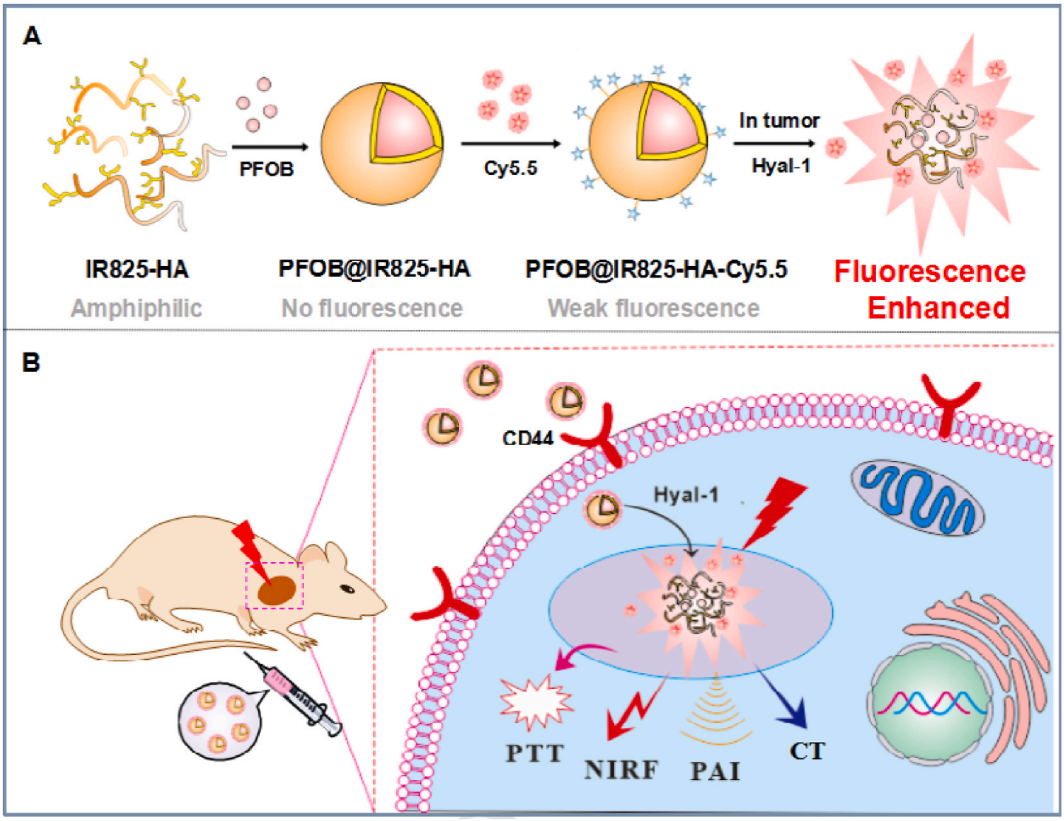


Fig. 8. Schematic representation of the (A) synthesis and (B) application of PFOB@IR825-HA-Cy5.5 NPs for triple imaging (fluorescent, photoacoustic, and computed tomography) and tumor ablation in HT-29 mice cells. "Reprinted from Ref. [74] with permission code of 5880090791756)".

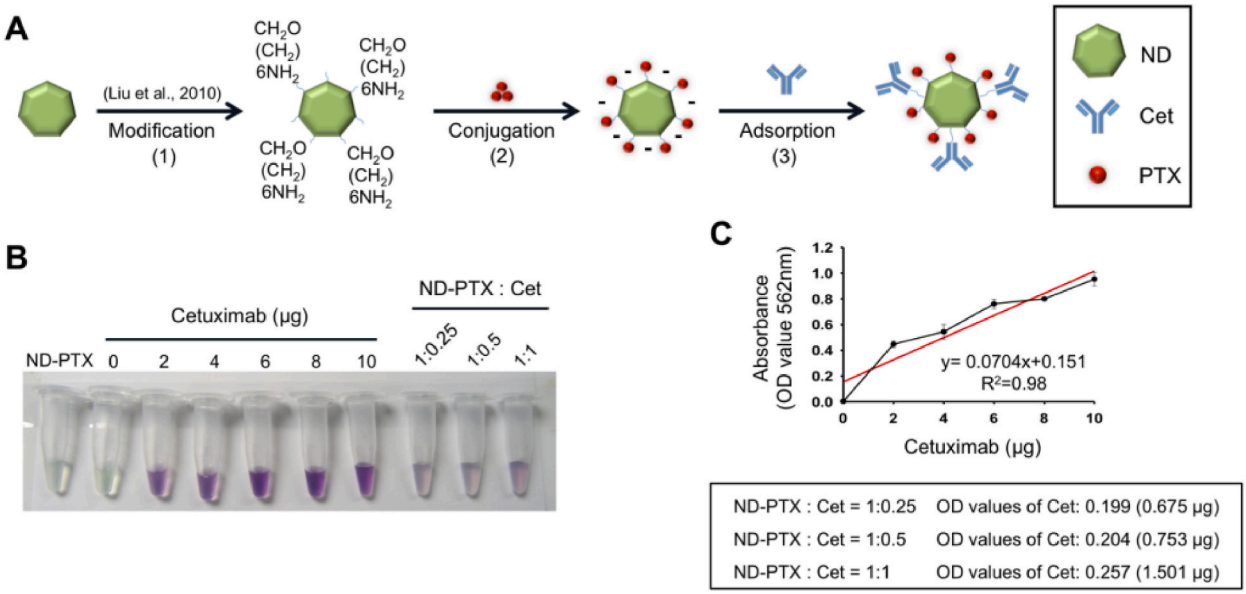


Fig. 9. A) Schematic illustration depicting the preparation of ND-PTX-Cet. B) Preparation of ND-PTX-Cet involved a simple mixture at 4 °C, followed by centrifugation at 12,000 rpm for 10 min at 4 °C. C) Evaluation of Cet loading efficiency on ND by comparing the OD values of ND-PTX-Cet with the standard curve to assess binding affinity. "Reprinted from Ref. [82] with permission code of 5880070179259)".

potential clinical application, Feng et al. injected tumor cells into mice and performed computed tomography (CT) and MRI. These imaging techniques showed enhanced contrast and accumulation of nanoparticles in engrafted cells, providing evidence for the effectiveness of this nanoprobe in cancer diagnosis. The nanoparticle was eliminated from the body through the renal pathway and displayed good biocompatibility. This finding demonstrates that it has minimal adverse effects on biological systems and the nanoprobe could be applied as a promising tool for cancer diagnosis and bioimaging techniques [80].

To combine anticancer drugs with nanoprobes, Nasrollahi et al. designed graphene quantum dots modified with the high-affinity single-chain variable fragment of the antibody (scFvB10) with EGFR through amide covalent linkages. They performed the nanoparticle on EGFR-positive MDA-MB-231 cell lines and used confocal microscopy and western blotting to confirm that the modified graphene quantum dots functioned well in bioimaging. Subsequently, they loaded cisplatin, a commonly used anticancer drug, onto these nanoparticles for therapeutic purposes. One notable feature of their nanoparticle design was its pH-dependent release mechanism. This pH sensitivity ensured that the release of cisplatin occurred primarily in the tumor microenvironment, thereby minimizing systemic cytotoxicity in normal cells. To test the selectivity of the nanoparticles, they saturated EGFR in a group of cells and then applied the modified nanoparticles, resulting in efficient cell death in unsaturated EGFR cells further highlighting the specificity and potential clinical utility of their approach. Consequently, this approach showed promise for both bioimaging and drug delivery [81].

In a similar study, Liao et al. designed a fluorescence emitting nanodiamond modified with EGF conjugated with two cytotoxic drugs: paclitaxel (ND-PTX) and Cetuximab (Cet) for triple-negative breast tumor cells (TNBC). The aim of this study was to target triple-negative breast tumor cells (TNBC) and evaluate the effectiveness of drug delivery. To assess the efficacy of this drug delivery systems, Liao et al. used different cell lines, namely MDA-MB-231 and MCF-7, and xenografted them into nude mice. The results indicated that the nanoparticles accumulated only in EGFR positive cells (MDA-MB-231) and successfully induced cell death. These finding provides promising evidence for the potential targeted therapy in treating triple-negative breast tumors (Fig. 9) [82].

In another study, Santana et al. developed nano-immunoconjugates with the aim of targeting the VEGF receptor. This was achieved through a combination of Ag-In-S/ZnS quantum dot, chitosan polysaccharide ligand, and monoclonal antibody. The researchers employed the green aqueous colloidal method to synthesize these conjugates, which were then tested on glioblastoma cells (U87), showing effective cellular uptake and potential for bioimaging and cytotoxic purposes [83].

Kim et al. designed a vesicle-shaped aptamer-coupled lysosome containing CdSe/ZnS quantum dots via the thin-film hydration technique. To enhance the delivery of therapeutic molecules, they added water-soluble siRNA to the complex through continuous mixing. The anti-EGFR aptamers were conjugated to the NPs and performed on MDA-MB-231 as the EGFR-positive and MDA-MB-453 as the EGFR-negative cells. To visualize the delivery of NPs to the cytoplasm of EGFR-positive cells, confocal fluorescent microscopy images were taken at various time points. The results from confocal fluorescent microscopy images showed successful delivery of NPs to the cytoplasm of the EGFR-positive cells, with a gradual increase in signal intensity over time. The delivery of NPs was dose-dependent, and the study also demonstrated the successful escape of siRNA from the endosome and its presence in the cytoplasm. The treated cells showed lower bcl-2 expression levels and eventual cell death. Bcl-2 is an anti-apoptotic protein often overexpressed in cancer cells, contributing to their survival and resistance to treatment. Tumor-bearing mice also showed signals accumulated on the tumor site, increasing 1-h post-treatment. This study presents a modified nanoprobe suitable for gene delivery and bioimaging applications [84].

In conclusion, overexpression of EGFR and VEGF is associated with malignancies with the epithelial origin and can facilitate the procedures involved in invasion and metastasis. This observation has led to the exploration of novel approaches for cancer diagnosis and bioimaging techniques that exploit these receptors. The studies discuss the development of nanoprobes that target cancer cells by exploiting epidermal growth factor receptors (EGFR) and vascular endothelial growth factor (VEGF) receptors. The studies involve the use of different nanoparticles, such as silicon nanoparticles, modified nanodiamonds, organic nanoparticles, graphene quantum dots, and quantum dots, loaded with anticancer drugs or bioimaging agents. The use of silicon nanoparticles as carriers for anticancer drugs or bioimaging agents. These nanoparticles can be functionalized with ligands that specifically bind to EGFR or VEGF receptors, allowing for targeted delivery to cancer cells. In addition, modified nanodiamonds have also been investigated as potential carriers for targeted therapy and bioimaging. These nanodiamonds can be loaded with anticancer drugs or fluorescent dyes, enabling simultaneous treatment and visualization of tumors. Organic nanoparticles have also shown promise in targeting EGFR and VEGF receptors for cancer diagnosis and therapy. These nanoparticles can be engineered to carry both imaging agents and therapeutic molecule. Furthermore, graphene quantum dots, which are small carbon-based nanoparticles, have emerged as another potential tool for targeted therapy and bioimaging. These quantum dots can be functionalized with ligands that specifically bind to EGFR or VEGF receptors, enabling selective delivery to cancer cells. Moreover, quantum dots themselves have intrinsic fluorescence properties, making them ideal candidates for bioimaging applications. The results show promise for the use of receptor-exploiting nanoprobes in cancer diagnosis, bioimaging, and targeted therapy for various types of cancer.

3.5. HER2

The presence of human epidermal growth factor receptor 1 or 2 (HER1/HER2) has been linked to the progression, invasion, angiogenesis, and metastasis of certain malignancies including breast, gastric, ovarian, and non-small cell lung cancers [85,86]. Tyrosine kinase inhibitors of HER1/2 can be the first-line treatment for these disease [87]. HER2-mediated delivery of nanoprobes is the way of labeling the malignant tissue. HER2-mediated delivery of nanoprobes is a technique used to label malignant tissue. Shengnan Liu and colleagues created two near-infrared fluorescent probes (Cy3-AFTN and Cy5-AFTN) that could inhibit both HER1 and HER2 by using afatinib, a dual HER1/HER2 tyrosine kinase inhibitor approved by the FDA for treating NSCLC metastasis and specific NSCLC with EGFR mutations. They designed a reversible noncovalent dual targeting probe that had cytotoxic effects against all

three cell lines tested (A549, SKOV3, and MCF7) and were selectively accumulated in xenograft tumor cells in vivo. The probes show potential for use in fluorometric screening of drug discovery [86].

Kanazaki et al. synthesized iron oxide nanoparticles (IONP) that were modified with anti-HER2 compounds, including peptides, single-chain fragment variable (scFv), and whole immunoglobulin G (IgG) in three different sizes (20, 50, and 100 nm). They tested these nanoparticles on N87 human gastric cancer cells that had high levels of the HER2 gene. The results showed that the scFv-conjugated IONP with a size of 20 nm (SNP20) had a strong binding affinity to HER2 receptors on the cells, making it an excellent contrast agent for photoacoustic imaging, a non-invasive imaging technique used in cancer diagnosis. Furthermore, the SNP20 had low cellular toxicity and low photobleaching [88]. These characteristics are crucial for any contrast agent used in bioimaging techniques as they ensure minimal harm to the cells being studied and maintain image quality over time. In a similar study, Zhang et al. created Herceptin-templated gold nanoclusters using the green synthesis method to preserve the three-dimensional structure of Herceptin (Fig. 10). These nanoclusters were tested on SKBR3 HER2-positive cell lines and in vivo in mice. The cell-binding assay showed that Her-Au NCs and pure Herceptin inhibited the cell binding of 125I-Herceptin in a concentration-dependent manner. Her-Au NCs had slightly higher uptake in the cells than Herceptin. The nanoparticles accumulated mainly in the liver and kidney, and radiolabeling with 125I enabled SPECT/CT imaging to track their metabolic behavior. Monoclonal antibody-based probes like Herceptin-templated gold nanoclusters can be used for in vivo imaging due to their photostability [89]. This approach offers a non-invasive method for visualizing the biodistribution and clearance of these nanoparticles. The use of molecular imprinting technique in combination with nanoparticle-based imaging and therapy offers several advantages. Firstly, it provides high selectivity and sensitivity towards specific targets. This allows for accurate detection and localization of cancer cells or tumors. Secondly, by incorporating therapeutic agents into these nanoparticles, targeted therapy can be achieved, minimizing off-target effects and improving treatment outcomes. For theranostic purposes, Wang et al. designed fluorescent silicon nanoparticles coated with a molecularly imprinted polymer (MIP) against the HER2 receptor and loaded with doxorubicin for theranostic purposes. The MIP recognized the HER2 receptor, and the SiNP produced excellent fluorescent images. The MIP-positive nanoparticles showed strong fluorescence and uptake in cells, and MIP@DOX effectively killed breast cancer cells. Molecular imprinting technique can serve as a targeted imaging and therapy agent with high selectivity and sensitivity [90].

In conclusion, the presence of HER1/HER2 is associated with the progression of certain malignancies, and tyrosine kinase

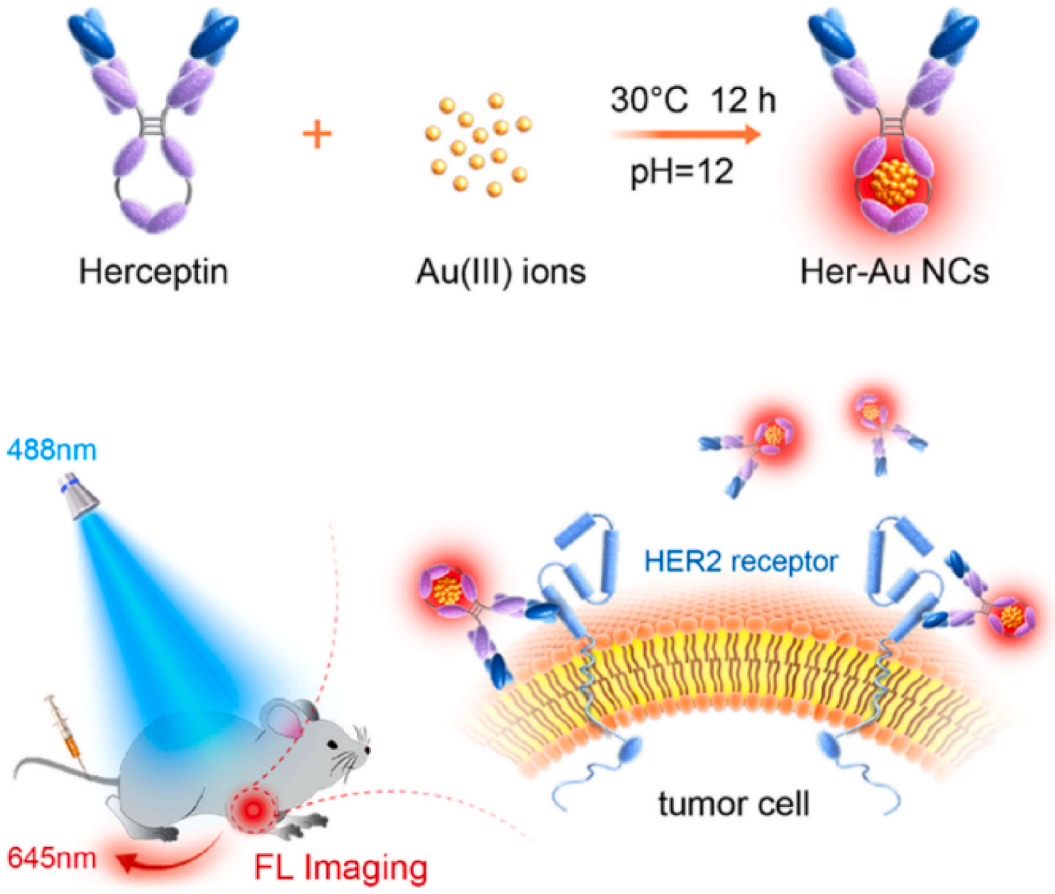


Fig. 10. Schematic representation illustrating the process of Her-Au nanoclusters (NCs) formation and their potential applications in HER2-Targeted imaging for cancer diagnosis. "Reprinted (adapted) with permission from Ref. [89]. Copyright 2024 American Chemical Society."

inhibitors can be used as treatment. HER2-mediated delivery of nanoprobes is a technique to label malignant tissue. Two near-infrared fluorescent probes that inhibit HER1 and HER2 were created, and iron oxide nanoparticles modified with anti-HER2 compounds were developed for photoacoustic imaging. Herceptin-templated gold nanoclusters and fluorescent silicon nanoparticles coated with MIP against HER2 were designed for in vivo imaging and therapy, respectively. These probes show potential for use in drug discovery and as targeted imaging and therapy agents.

3.6. Plectin-1

Pancreatic ductal adenocarcinoma (PDAC) represents a significant contributor to mortality rates in the United States, presenting as a formidable challenge in clinical practice. The resistance nature of pancreatic cancer to conventional treatment modalities, such as chemotherapy and radiotherapy, coupled with the limited efficacy of surgical interventions (operative success rates ranging from 10 % to 25 %) due to the extensive infiltration of adjacent structures at the time of diagnosis, underscores the formidable clinical hurdles faced in managing this disease. Consequently, the overall prognosis for patients afflicted with PDAC remains bleak, necessitating a deeper understanding of the molecular mechanism underlying the pathogenesis of this aggressive malignancy [91].

Plectin-1 is a high molecular weight protein with a mass of approximately 500 kDa. Plectin-1 is characterized by its structural composition, comprising three principal components-microtubules, microfilaments, and intermediate filament [42]. Studies have indicated that plectin-1 exhibits aberrant expression patterns in the cellular membrane of PDAC cells, with a remarkable 93 % of PDAC cases demonstrating positivity for this protein. The dysregulated expression of plectin-1 in PDAC not only implicates its involvement in the pathogenesis of the disease but also correlates significantly with poorer prognostic outcomes for affected individuals [92].

In numerous investigations focusing on pancreatic cells, the plectin-1 targeted peptide emerges as a prominent focal point. For example, Wang et al. undertook the synthesis of bovine serum albumin (BSA) combined with superparamagnetic iron oxide nanoparticles (SPIONS) and anti-plectin-1 monoclonal antibodies (mAbs). This bioconjugate was then employed in the targeting of PDAC cells, yielding discernible outcomes in terms of accurate identification of plectin-1 through both fluorescent and magnetic resonance imaging (MRI) modalities [93]. This approach presents several key advantages, including high biocompatibility, colloidal stability, and high relaxivity. For instance, in a study conducted by Chen et al., a plectin-1 targeted multi-functional SPIONS was designed and evaluated in vitro. This nanoparticle was formulated with 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-amino(polyethylene glycol) (DSPE-PEG-NH2) and conjugated with lectin-1 antibody and/or Cy7, resulting in a nanoparticle of 84 nm in size. The findings from this study demonstrate the efficacy of the plectin-1 targeted fluorescence and MR dual-functional nanoparticle in visualizing PDAC cells using different probes. Moreover, the utilization of surfactants such as polyethylene-glycol (PEG) to modify SPIONS in certain studies has been shown to prolong the blood circulation of Near Infrared Fluorescent agents (NIRF). This extended circulation time enhances the effectiveness of the nanoparticles in targeted imaging applications. Additionally, the hydrodynamic size of nanoparticles, typically ranging between 10 and 100 nm, plays a pivotal role in promoting high blood circulation. Furthermore, nanoparticles within this size range exhibit enhanced liver uptake and are more readily able to reach target sites efficiently [42].

The practice of antibody targeting in molecular imaging often faces challenges, such as suboptimal pharmacokinetics resulting in a limited target-to-background ratio and a restricted capacity for carrying out magnetic resonance (MR) unless detectable imaging is employed. To address these issues, Kelly et al. pioneered the development of peptides that specifically bind to cell surface antigens on PDAC cells using a phage display technique. Among these peptides, the plectin-1 targeted peptide (PTP) with the amino acid sequence KTLLPTP was identified. Through the conjugation of these peptides to magnetofluorescent nanoparticles, the detection of small PDAC and precursor lesions was significantly enhanced in engineered mouse models. This innovative approach not only facilitated the rapid identification and validation of PTP but also demonstrated substantial promise for future clinical applications [92].

4. Clinical consideration of application of nanomaterials for bioimaging

One of the significance of nanoparticles in biomedical applications stems from their small size, which confers distinctive properties. However, it is crucial to acknowledge that this very small size presents inherent risks to human health due to the potential for NPs to evade immune detection and even traverse physiological barriers, such as the blood-brain barrier. While the primary mode of administration for NPs in bioimaging applications is through intravenous injection, the implication of their size on diffusion properties within biological systems cannot be overlooked [22].

The size of particles or molecules directly influences their diffusion behavior within biological samples. Smaller materials exhibit enhanced diffusion rates within physiological environments. Furthermore, the surface functional groups of fluorescent materials play a pivotal role in dictating their bioavailability and transport mechanism across cellular membranes and tissues, necessitating thorough consideration before clinical implementation. Moreover, the size of fluorescent materials plays a critical role in determining the achievable resolution of imaging techniques, especially in scenarios where super-resolution imaging is essential [11,94].

Nanomaterials exhibit a wide range of size distributions based on synthesis conditions, posing significant implications within biological systems. A critical consideration is the hydrodynamic radius, influenced by the ligand and functionalization processes of nanomaterials. The determination of the hydrodynamic radius often stems from dynamic light scattering experiments, a common method employed in such analysis. Furthermore, the concept of protein corona emerges as a critical factor in biological contexts. Within biological fluids like serum or blood, proteins tend to adsorb nanoparticles creating a protein corona around the particle. This phenomenon plays a pivotal role in understanding the interactions and effects of nanomaterials within biological systems. In addition, the uptake of nanomaterials by phagocytic cells holds significant effects. These interactions greatly impact the particles' hydrodynamic radius, diffusion properties, and specific target analytes. The consequential interactions and potential accumulation or interference are

integral considerations, particularly in the context of contrast agents [9,11].

Despite the promising potential of nanostructured contrast agents, certain limitations hinder their clinical applicability. Issues such as slow renal clearance and non-specific accumulation in mononuclear phagocyte systems continue to impede their widespread use. This highlights the importance of further research and development to address these challenges.

Visible light, ranging from 400 nm to 650 nm, faces significant attenuation when passing through tissues due to the presence of substances like collagens, hemoglobin, and lipids. These factors contribute to the limitation of visible light penetration into deeper tissue layers. Additionally, various biological molecules such as collagen, NADPH, fatty acids, falvins, and porphyrns exhibit strong auto-fluorescence across the visible light spectrum, further complicating imaging and analysis procedures. In response to these challenges, a crucial strategy for enhancing clinical applications involves shifting the focus toward near-infrared biological windows. By moving towards wavelengths between 650 nm and 950 nm and 1000 nm–1350 nm, significant improvements in tissue penetration capabilities can be achieved. The utilization of light within these near-infrared ranges enables deeper tissue penetration compared to visible light. Furthermore, the spectral regions of 950 nm and 1350 nm offer the advantages of reduced endogenous fluorescence from biomolecules. The diminished auto-fluorescence in these specific regions creates a more favorable environment for clinical applications, allowing for clearer imaging and analysis outcomes [11,95]. Another important criterion in bioimaging is the surface chemistry of fluorescent nanomaterials. A fluorescent nanomaterial typically comprises three primary components: a nanoparticle core, a layer of surface groups or molecules (known as ligands), and a biofunctionalization layer. The need for a biofunctionalization step affects the composition of the nanoparticle core. For instance, silica nanoparticles commonly bear hydroxyl groups on their surface in the absence of functional groups. Consequently, the functionalization of silica NPs with amine groups becomes imperative to facilitate their covalent binding with proteins or antibodies targeting cancer cells. On the contrary, semiconductor quantum dots are often synthesized with ligands alone, without the inclusion of a specific biofunctionalization agent. Nonetheless, instances exist where a biofunctionalization step becomes necessary to modulate particle solubility or enhance the attachment process [11].

The criticality of designing fluorescent nanomaterial that exhibits water solubility and stability under physiological conditions or in serum cannot be overstated. For example, the encapsulation of hydrophobic dyes within polymer particles represents a viable approach to rendering them water-soluble in an aqueous milieu. Notably, semiconductor quantum dots and rare-earth-based materials are typically synthesized in organic solvents, underscoring the importance of functionalizing them with hydrophilic molecules such as organosilane species [94].

Assessing the toxicity of nanomaterials in biological environments, such as cell membranes or target-specific biomolecules, presents a complex challenge due to the ability of nanomaterials to circumvent natural barriers. Nanomaterials engage with and impact biological systems in regions where essential biological processes occur. For example, these interactions occur during cell proliferation and gene expression alterations, culminating in the sequestration of nanomaterials in these regions. Consequently, this leads to immune responses being triggered or molecular transport within cells impacted. The nature of these interactions and effects between nanomaterials and biological systems is predominantly contingent on various factors, including the size of nanomaterials, their concentration, and the surface functional groups they possess. These factors not only influence processes like endocytosis and cytotoxicity of the particles but also determine the clearance pathways through which nanomaterials are eliminated from an organism, such as excretion via the kidneys or metabolism in the liver.

Considering the multifaceted influence of nanomaterial properties on their interactions within biological systems, the assessment of nanomaterial toxicity is inherently intricate. However, in certain instances, the incorporation of toxic substances like selenide and heavy metals into nanomaterials can result in adverse effects unless appropriate measures are taken to encapsulate these materials with a protective layer [11,22].

The utilization of fluorescent nanoparticles in bioimaging applications has predominantly been explored in studies conducted on a small laboratory scale using animal models rather than in contexts directly relevant to human application. Such a focus on animal models necessitates meticulous monitoring and control of various parameters to ensure meaningful and translatable outcomes. Critical considerations in animal studies involve the management of factors such as the duration of anesthesia, monitoring of physiological parameters including temperature, respiration rate, and cardiac activity, as well as vigilance towards potential side effects, signs of discomfort or distress, and technical intricacies like establishing vascular access and accounting for the limited blood-pool volume typical in small animals.

Transitioning from the preclinical evaluation phase in animal models to the clinical application in human subjects demands a comprehensive assessment of numerous key aspects. These include but are not limited to evaluating the biocompatibility and non-toxicity of the fluorescent nanoparticles, assessing their stability under physiological conditions, determining their fate within living systems, investigating their long-term impacts on patient health, ensuring their efficacy in achieving the intended imaging outcomes, managing costs associated with implementation, and navigating the regulatory approval process such as obtaining clearance from the Food and Drug Administration (FDA) [94].

The production of fluorescent nanomaterials poses unique challenges compared to small molecule agents, often requiring complex formulations and involving multiple components. This complexity complicates the scalability of manufacturing processes for fluorescent nanomaterials, particularly when considering their application in larger-scale commercial production within clinical settings. Therefore, a critical factor to be weighed in the utilization of fluorescent nanomaterials is their cost-effectiveness, as the intricate production requirements can significantly impact the economic feasibility of implementing these materials in clinical practice. Despite the potential cost challenges associated with producing fluorescent nanomaterials, their utilization offers a myriad of compelling benefits that can rationalize the investment. One notable advantage is the enhanced capability of fluorescent nanomaterials to facilitate early detection of various medical conditions, with a particular emphasis on their utility in detecting cancer at its nascent stages [13].

Various strategies have been suggested to rationalize the expenses associated with the production of fluorescent nanomaterials. One prominent approach involves the development of multi-functional fluorescent nanomaterials, which have the potential to serve as tailored imaging agents for personalized medicine applications. These specialized nanomaterials exhibit the capability to identify distinct tumor subtypes within highly heterogeneous tumors by recognizing specific genetic or epigenetic markers through both in vivo and *ex vivo* diagnostic modalities. Moreover, the capacity to integrate fluorescent nanomaterials with other imaging modalities such as MRI, CT, PET, and optical imaging, among others, presents a compelling rationale for reducing overall costs while concurrently enhancing diagnostic precision, selectivity, and sensitivity. This synergistic coupling of fluorescent nanomaterials with diverse imaging techniques not only streamlines the diagnostic process but also augments the accuracy and effectiveness of disease identification and monitoring [13,95].

5. Conclusions and future outlooks

In conclusion, cancer remains a significant global health concern, and the development of precise diagnostic and therapeutic tools is crucial for effective management. Bioimaging techniques have emerged as valuable non-invasive methods for studying biological processes with minimal interference, which can overcome limitations of conventional methods. This review summarizes different cellular membrane receptors as a theranostic tool conjugating with nanoparticles for bioimaging technique. Various types of nanoparticles have shown promise in improving imaging techniques. These nanoparticles offer enhanced imaging capabilities and therapeutic applications due to their excellent features like high loadable surface, photostability, selectivity entrance to the cell, and biocompatibility. Carbon-based fluorescent nanomaterials were frequently utilized for fabricating bioimaging probes which mainly caused by their high compatibility. Also, metallic materials were also employed for designing bioimaging platforms in which biocompatible materials were used for surface modification to regulating cellular toxicity. Also, some nanoparticles were utilized to improve the contrast and brightness of images by penetration into cells. Application of nanoparticles for bioimaging poses some challenges, including contamination, insufficient batch-to-batch variability, chemical instability, biocompatibility, low production and quantum yield, high cost of production, and lack of infrastructure, leading to bioimaging techniques based on nanomaterials mostly remaining in clinical trials. Some challenges are as follows.

a) Applying nanoparticles for bioimaging requires non-toxicity and biocompatibility. The interaction between nanoparticles and biological systems should not induce any adverse effects or toxicity. Using surface modification with a ligand binding to the target (the receptor) can reduce toxicity.
b) Low production yield and scalability complexities are additional challenges that need to be addressed. Nanoparticles manufacturing processes often suffer from low production yields, making it difficult to produce sufficient quantities for clinical trials. Furthermore, scaling up the manufacturing process can introduce additional complexities and challenges. Therefore, optimization of manufacturing processes and the development of scalable production methods are necessary to overcome these limitations.
c) High cost is another significant challenge in nanoparticles manufacturing. The complex nature of nanoparticles formulations and the specialized equipment required for their production contribute to high manufacturing costs. These high costs can hinder the progress of clinical trials, as they may limit the availability of the drug for testing in a larger patient population. Therefore, efforts should be made to optimize manufacturing processes and reduce production costs without compromising on quality.
d) It is important nanoparticles possesses high selectivity and low sensitivity to temperature, except to temperature dependence systems.
e) It is important to consider regulatory approval before applying nanoparticles for bioimaging purposes and monitor nanoparticles continuously in blood circulation, study physiological barrier penetration.

However, these nanoparticles can be promising next-generation theranostic agents. Further research and development in this field are necessary to advance the understanding and application of these nanoparticles.

CRediT authorship contribution statement

Tooba Mohammadi: Writing – original draft, Investigation, Formal analysis. **Hadi Gheybalizadeh:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Elaheh Rahimpour:** Writing – review & editing, Conceptualization. **Jafar Soleymani:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Vahid Shafiei-Irannejad:** Writing – review & editing, Supervision, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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