Chapter

Theranostic Nanoparticles and Their Spectrum in Cancer

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Abstract

Nanoparticles offer a lot of advantageous backgrounds for many applications due to their physical, chemical and biological properties. Their different composition (metals, lipids, polymers, peptides) and shapes (spheres, rods, pyramids, flowers and so on) are influenced by the synthesis methods and functionalization procedures. However, in the medical field, researchers focus on the biocompatibility and biodegradability of the nanoparticles in their attempts for a targeted therapy in which the nanocarriers need to bypass certain biological barriers. Moreover, the increased interest in molecular imaging has brought nanoparticles in the spotlight for their applications in two distinct directions: therapy and diagnosis. Furthermore, recent advances in nanoparticle designs have introduced novel nano-objects suitable as both detection and delivery systems at the same time, thus providing theranostic applications.

Keywords: nanoparticles, nano-oncology, targeted therapy, molecular imaging, diagnosis

1. Introduction

Nanomedicine is able to study the organism and especially the disease at the nanoscale level and offers a lot of structural and functional information for the development of new therapeutics and diagnosis strategies [1]. Nano-oncology refers to the applications of nanotechnology in the oncology medical field.

Oncological malignancies affect worldwide population with an incidence of 18.1 million new cancer cases and 9.6 million cancer deaths (GLOBOCAN 2018). Usually, the most used treatment scheme is surgery, radiotherapy and chemotherapy. These strategies are not very efficient because it does not only affect the disease site, but healthy tissues too, and in many cases, cancer can develop therapy resistance [2].

Nanotechnology tools have potential to overcome the side effects and the inefficiency of some therapies. Due to its small size, nanoparticles (NPs) can be used for molecular characterization of the disease, and based on this, it can contribute to discover new therapies. Moreover, various oncological chemotherapeutics are nanoformulated and now are involved in clinical trials [3].

Besides drug encapsulation, NPs can be used for the delivery of growth factors and other compounds applied in tissue engineering. On the other hand, NPs' properties are advantageous for new sensing and molecular imaging tools development (**Figure 1**).

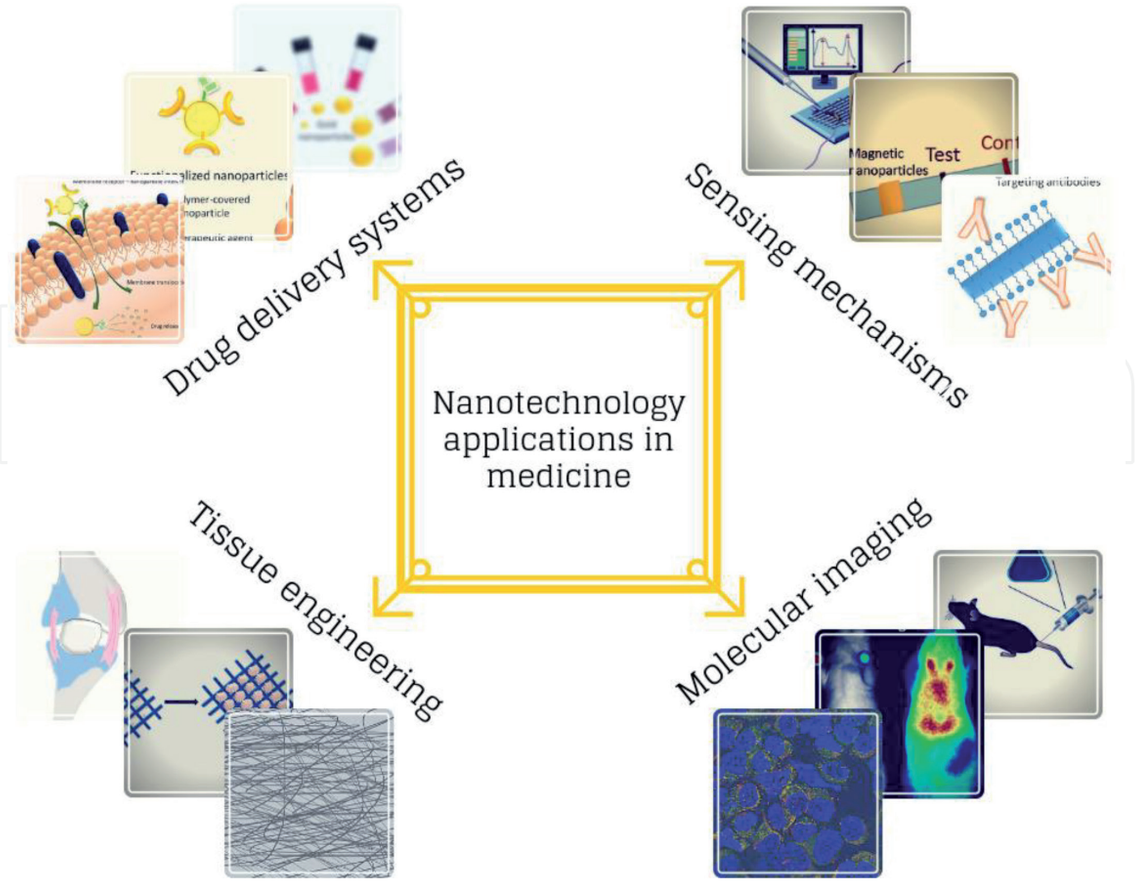

Figure 1.
Nanotechnology applications in medicine.

For each of these applications, NPs' formulations involve various encapsulation procedures, which need to meet specific characteristics. Firstly, the NPs should not interfere with the encapsulated compound pharmacological activity, and it has to prevent its premature degradation and to become biodegradable at the tumor site, thus decreasing its toxicity [4]. Secondly, for sensing applications, the nanosystem needs to have some unique chemical, electrical, and catalytical properties to provide accuracy of the measurements [5]. On the other hand, for molecular imaging applications, the NPs benefit from their optical properties like fluorescence in various spectra. Also, the features such as biocompatibility, stability and long circulation time are very important [6–8].

Theranostic side of the nano-oncology field focuses on developing new structures that able to perform efficient target therapy. Therefore, this type of NPs disposes of unique physical and chemical properties for active targeting of the desired cells providing imaging and therapeutic action against the disease [8].

2. Nanoparticles

The term "nanoparticles" is intensively used in the nanomedicine field in order to describe a particle with a size in the range of 1–100 nm. NPs are designed from a wide class of materials, including metals, silicates, metal oxides, polymers, organics, non-oxide ceramics, carbon and biomolecules. For biomedical applications, NPs are presented in different morphological states such as spheres, tubes, cylinders, platelets [9].

NPs have surface modifications that can facilitate the internalization/uptake of therapeutic agents and also their capability to travel through the bloodstream to the target sites. Generally, the structure of NPs is composed of three different

layers, including the surface layer (can be functionalized with a wide range of small molecules, surfactants, metal ions and polymers), the shell layer (consists of different chemical material according to the core of the NPs) and the core (represents the central portion of the NP) [10]. Therefore, NPs have exceptional characteristics due to their structure and design and gained an enormous interest in multidisciplinary fields such as drug delivery [11], cancer therapy, tissue engineering, protein detection, multicolor optical coding for biological assays, manipulation of cells and biomolecules [12], imaging, biosensors, hyperthermia, photoablation therapy and gene delivery [13]. They exhibit special physical and chemical properties like a high surface area-to-volume ratio and also a unique quantum size effect superior to their corresponding bulk materials. Moreover, NPs' controllable size and shape play an important role in medical applications [14]. Moreover, there are some nanomaterials that can exhibit intrinsic therapeutic properties such as gold nanoshells, which have the potential to deliver photothermal therapy [15].

Currently, the term "theranostics" starts to gain attention in the medical and research field, and it describes single biocompatible and biodegradable nanoparticle, which can contain both therapeutic and diagnostic compounds (**Figure 2**) [16]. Specifically, theranostic nanoparticles (TNPs) have been designed in order to be applied for multiple imaging approaches including optical imaging, ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), single-photon computed tomography (SPECT) and positron emission tomography (PET) [17]. Moreover, TNPs are able to improve the accumulation and delivery of the active compounds at the tumor site, enhancing therapeutic efficacy and reducing the intensity of side effects on healthy tissues [18], and they can be eliminated from the body in a short period of time and degrade into nontoxic bioproducts [19].

2.1 Synthesis of NPs

Synthesis of NPs can be performed using various methods, which are divided into two main classes such as bottom-up (chemical synthesis) and top-down (mechanical attrition) approaches (**Figure 3**) [20]. Bottom-up method is based

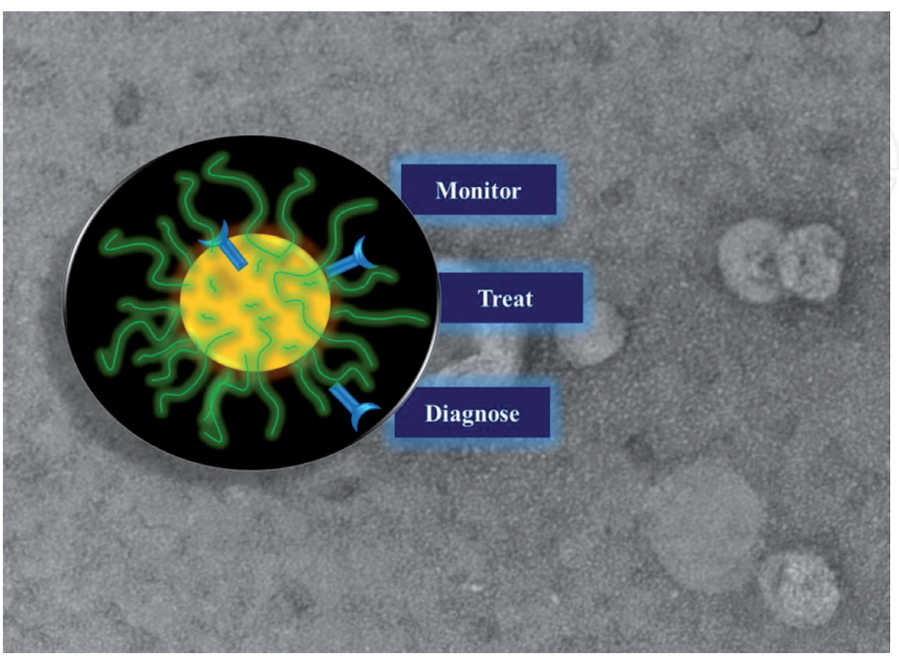

Figure 2.
Theranostic nanoparticles used in the medical field in order to improve the diagnosis and therapeutic approaches.

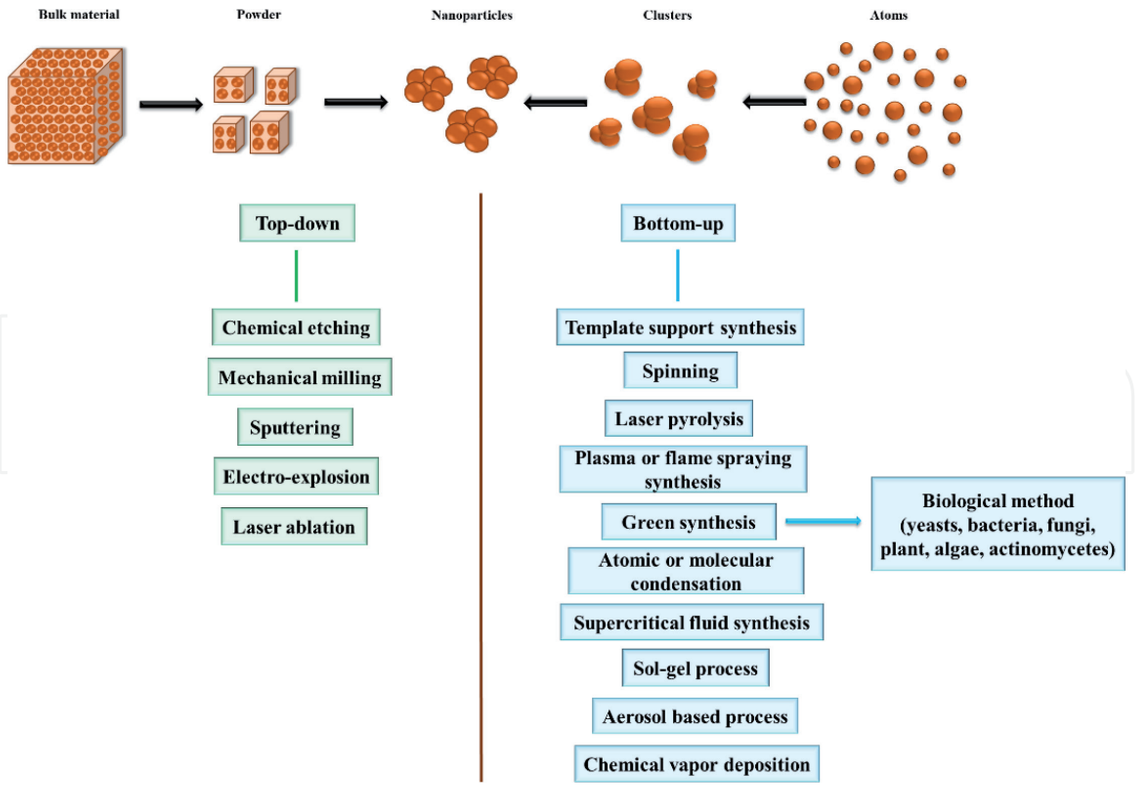

Figure 3.
Common methods used to synthesis NPs via top-down and bottom-up approaches.

on larger nanostructures design beginning from smaller building blocks including atoms and molecules. Meanwhile, the top-down approach refers to larger molecules, which are decomposed into smaller building blocks and then converted into suitable NPs [10]. Traditional chemical and physical methods present some main drawback due to the presence of reducing and stabilizing agents, which carry a risk of toxicity to the environment and also to the cell [21].

Currently, green chemistry has been suggested as a valuable alternative for metal nanoparticles synthesis that employs biological entities including microorganisms and plant extracts [22]. The main role of microorganisms (bacteria and fungi) is involved in the remediation of toxic materials by reducing metal ions [23]. The most often used metal for green synthesis is silver, gold, iron, and copper [24]. Therefore, the size distribution of NPs is strongly depended on the presence of the biocompounds, which are found in the extract. These biocompounds (phenolic compounds, alkaloids, enzymes, terpenoids, proteins, co-enzymes, sugar and others) are mainly involved in reducing the oxidative state of the metal salts from positive to zero oxidative state [25]. Few bacteria have been shown the potential to synthesize silver nanoparticles intracellularly where intracellular components have the ability to act as reducing and stabilizing agents, respectively [26]. Thus, the green synthesis of nanoparticles could be a promising approach to replace many complex physiochemical syntheses due to their advantages such as no need to use toxic chemicals, free from hazardous by-products and also the use of natural capping agents [27].

In their study, Mirtaheri et al. had succeeded in synthesis of mesoporous tungsten oxide using a template-assisted sol-gel method, which relies on the photocatalytic degradation of Rhodamine B [28]. Mesoporous TiO_2-SiO_2 were synthesized by Haghighatzadeh et al. using an ultrasonic impregnation method. In addition, under 800°, they synthesized the anatase crystals with higher photocatalytic efficiency for degradation of methylene blue [29]. Deshmukh et al. synthesized various nanoparticles using plant extracts in order to evaluate their antibacterial and antioxidant

activity for targeted applications [30]. Another study on this topic is showed by Baltazar-Encarnacion et al., which described the green synthesis of Ag nanoparticles using an *E. coli* for the production of NPs with antimicrobial properties against bacteria [31]. Green biosynthesis methods are more reliable and safer than chemical synthesis [32].

Structural DNA nanotechnology is a precise method, which is used to control the NPs shape. In particular, the DNA-origami method allows the controlled self-assembly of 2D and 3D nanostructures with nanometer precision [33]. Such nanoparticles can be used to detect short oligonucleotides in a microbead-based assay [34] and can be applied in the biological field, nanoelectronics and nanophotonics [35]. Therefore, these designs provide comprehensive understanding of cellular interactions regarding tumor detection strategies [36, 37].

Specifically, TNPs can be engineered in several ways. For example, TNPs can be obtained by conjugating therapeutic agents (chemotherapy and photosensitizers) to existing imaging NPs (quantum dots, gold nanocages and iron oxide NPs). On the other hand, NPs can encapsulate both imaging and therapeutic agents in biocompatible nanosystems such as ferritin nanocages, polymeric and porous silica NPs. Other unique NPs such as porphycenes, [64Cu] CuS, gold nanoshells or cages have inherent imaging and therapeutic characteristics [19].

2.2 Characterization of NPs

Physicochemical properties of NPs (shape, size, composition, optics) can be analyzed through different techniques.

The morphology of NPs is characterized through microscopic techniques including polarized optical microscopy (POM), transmission electron microscopy (TEM) and scanning electron microscopy (SEM), which are the most relevant techniques in this area. SEM technique provides relevant information regarding the nanoscale level of the NPs [38]. Moreover, TEM provides features about the bulk material used for NPs synthesis at very low to higher magnification [39]. The morphological features of the NPs exhibit a relevant interest since their morphology influences the NP's properties [10].

Structural characterization is based on the study of the composition and nature of bonding materials. The common techniques used to study the bulk properties are X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), infrared spectroscopy (IR), Raman, Brunauer-Emmett-Teller (BET), energy dispersive X-ray (EDX) and Zeta size analyzer. Through XRD technique, the crystalline structure and the phase of the NPs are identified. The most sensitive technique used to characterize NPs is XPS, which determines the exact element ratio and bonding nature of the elements used for NPs synthesis [10].

Optical characterizations are widely used to obtain information about the absorption, reflectance, phosphorescence and luminescence of NPs. This method is based on the Beer-Lambert law and basic light principles. These properties are highlighted through several techniques, including diffuse reflectance spectroscopy (DRS), UV and UV-Vis, which reveal good knowledge about the mechanism of their photochemical processes [10].

2.3 Physicochemical properties of NPs

For cancer research, NPs can be modified respecting the size, shape and surface to improve their ability to reach tumors. Smaller NPs have the ability to accumulate more easily in the leaky blood vessels of tumor sites compared to larger NPs, which can remain at the injection site [40].

Nowadays, ultrasmall nanoparticles (1–3 nm cores) are widely used for medical applications because of their advantages regarding biodistribution, targeting features, adsorption, easy surface modifications and pharmacokinetics [18, 41–43]. Gadolinium ultrasmall nanoparticles achieved theranostic potential without considerable toxicity *in vivo* in the case of brain cancers [44]. Another example is represented by ultrasmall silica nanoparticles functionalized with antibody fragments used to target HER2-overexpressed breast cancer as imaging agents [42].

Metallic nanoparticles can be designed as ultrasmall constructs too. In this regard, it is important to mention D-peptide p53 activator gold nanoparticle conjugates used for cancer target therapy [45], bimetallic nanoparticles for triggered ultrasound cancer therapy [46] and Cu ultrasmall nanoparticles' valuable ability for photothermal cancer therapy [47].

On the other hand, NP shape influences the fluid dynamics and uptake into tumor sites. Non-spherical NPs present excellent optical properties due to surface plasmon resonances and are strongly recommended for cancer phototherapy applications [48–50]. Furthermore, rod-like shape nanoparticles are better accepted and tolerated by the organism [51, 52].

Specifically, spherical NPs started to be more common than non-spherical NPs due to challenges in synthesis approaches and testing [53]. Spherical silver nanoparticles ensure anti-inflammatory potential [54] and promote camptothecin apoptotic activity in cervical cancer [55]. Despite the advantages offered by silver nanoparticles, progress in spherical gold nanoparticles makes possible their use for combined therapies like drug delivery and photothermy [56].

There are other significant factors that contribute to a successful therapy development. Stability and distribution are affected by NPs charge. A positive charge is most effective according to tumor vessels targeting, but a switch to a neutral charge allows NPs to diffuse to the tumor sites [57]. In order to prolong blood circulation of NPs, their surface can also be modified with specific molecules (hydrophilic polymers/surfactants, biodegradable copolymers such as polyethylene glycol, poloxamine, polyethylene oxide and polysorbate 80), which facilitate cellular uptake into tumor tissue [58, 59].

2.4 Classification of NPs

Modern nanosystems can enhance drug diagnosis, delivery and also monitor therapeutic responses to the provided drugs [60]. In order to improve clinical outcomes, researchers tried to synthesize a theranostic platform consisting of multifunctional NPs, which exhibit valuable imaging properties. Therefore, TNPs can be composed of lipids, polymers, metals, carbon and ceramics [61].

Lipid nanoparticles are widely used in medical field due to their biodegradability, biocompatibility, low toxicity and high loading capacity for both hydrophobic and hydrophilic drug molecules [62, 63]. Moreover, they can improve the pharmacodynamics and the pharmacokinetics of therapeutic agents based on controlled release profile [64]. Another important characteristic of lipid NPs is their availability for functionalization with antibodies, peptides, small molecules or aptamers in order to perform target therapy [65–67].

Polymeric NPs are normally organic-based NPs with a diameter lower than 1 μm. They can be called nanospheres or nanocapsules depending on their composition [68–70]. These nanoparticles have the ability to improve both the solubility and the bioavailability of hydrophobic drugs [71] and are intensively used as delivery systems [72, 73].

Metallic NPs are designed from metal precursors, including noble metals (Cu, Ag, and Au). The most researched area in biomedical field is represented by gold

NPs, which possess unique optical and electronic characteristics as well as chemical inertness. Also, their availability for surface functionalization [74–76] makes them very useful for a lot of medical applications such as biosensing [77], bioimaging [78] and photothermal therapy [79]. Silver nanoparticles exhibit unique properties such as thermal conductivity, high electrical conductivity, catalytic activity, chemical stability, antibacterial and improved optical properties [80]. These NPs are suitable for photonic [81], electronic [82], antimicrobial and disinfectant applications [83, 84], biosensors [85], drug delivery, photothermal therapy [26] and cellular imaging [86].

Another class of metallic nanoparticles is represented by semiconductor nanocrystals, which are well known as quantum dots. Many studies report their potential use in biomedical imaging [87], drug and gene delivery [88] and also in diagnosis [89] based on their unique chemical and optical properties.

Magnetic NPs represented by iron oxide NPs possess unique chemical, biological and magnetic characteristics including non-toxicity, chemical stability, biocompatibility, high magnetic susceptibility and high saturation magnetization [90, 91]. The main drawback of iron nanoparticle is that it has a tendency to oxidize [13]. To eliminate this unwanted process, coating with a biocompatible shell, such as a polymer [92], ceramics [93] or metals [13], is needed in order to prevent conglomeration. In addition, iron oxide NPs can be functionalized with proteins, antibodies, enzymes and anticancer drugs [13] and are investigated for different applications including magnetic hyperthermia [94], contrast agents in MRI (magnetic resonance imaging) [95], targeted drug delivery [96], multimodal imaging and gene therapy [61].

In the term of carbon-based NPs, fullerenes and carbon nanotubes exhibit promising biomedical applications. Fullerenes are suitable for multiple functionalization steps according to their particular globular network structure [97]. They are widely used as excellent antioxidants [98], antiviral agents [99, 100], drug and gene delivery systems [101–103] and photosensitizers for photodynamic therapy [104, 105]. On the other hand, elongated design of carbon nanotubes diagnostic imaging strategies [107–110], drug delivery [111–113] and also photothermal therapy [114, 115].

Ceramics NPs are inorganic non-metallic solids, which are synthesized by heating and successive cooling [116]. Therefore, these ceramics NPs are intensively used in the research field as photocatalysis, catalysis, agents for photodegradation of dyes and imaging agents [117].

There are significant challenges in engineering and designing new nanosystems. The "nanoparticle loaded nanoparticle" concept is described as an innovative strategy composed of at least two different nanoparticles. For example, porous nanoparticles made by silica can encapsulate DNA-conjugated small gold nanoparticles in their pores with great applicability in penetrating tumors [118].

Hybrid constructs gained increased interest in obtaining programmed nanoparticles. DNA nanorobots built of a DNA robot and a DNA aptamer that confers molecular recognition of nucleolin are used for target therapy in cancer [119].

3. Cellular internalization and endosomal escape

Once the delivery system comes in the proximity of its target site, the drug must be internalized in order to fulfill its biological effect. While free drugs usually have the ability to pass through cellular membranes and accumulate inside the cell unless they are externalized by efflux pump mechanisms, NPs are internalized differently, mainly through various types of endocytosis [120], as presented in **Figure 4**.

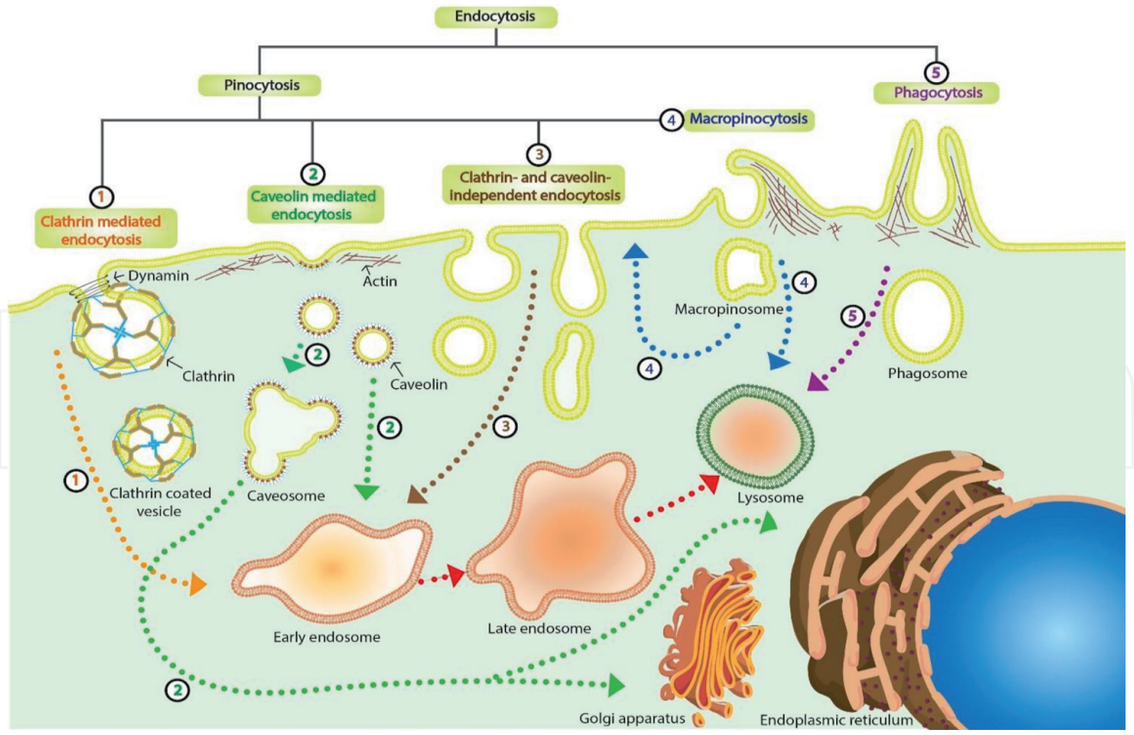

Figure 4.
Cellular internalization through endocytosis.

Phagocytosis is a mechanism by which specialized cells known as phagocytes recognize and engulf large particles (≥0.5 μm) into vesicles called phagosomes [121]. This process involves actin polymerization and the extension of pseudopods, which surround the opsonized target object [122] leading to its internalization (**Figure 4(5)**). Phagosomes fuse with early endosomes, followed by late endosomes and then lysosomes, becoming highly acidic and possessing hydrolytic enzymes leading to the degradation of the engulfed object [122].

Macropinocytosis is a process by which nonselective molecules suspended in extracellular fluid are internalized into the cell, giving rise to endocytic vesicles. Like phagocytosis, it involves cytoskeleton rearrangement beneath the plasma membrane. This leads to a plasma membrane circular ruffle formation that extends and entraps extracellular material, producing a so-called macropinosome [123]. The maturation of these vesicles involves shrinking while concentrating their contents, migration and digestion or recycling of their contents [124]. Depending on the cell line, macropinosomes can fuse with lysosomes or directly to the plasma membrane expelling their content to the extracellular space (**Figure 4(4)**) [124, 125].

Caveolae are small (60–80 nm) plasma membrane invaginations, important in processes such as endocytosis, transcytosis, potocytosis and certain signaling pathways [126]. Caveolin-dependent endocytosis is a triggered, energy-dependent event involved in the uptake of extracellular molecules and membrane components [127]. It is dependent on actin and dynamin, a GTPase, which is present at the neck of caveolae and is responsible for the release of the caveolar vesicle inside the cytoplasm [128]. These vesicles deliver the internalized molecules to caveosomes or to early endosomes (**Figure 4(2)**). Caveosomes bypass lysosomes, thus being an important approach for administering easily degradable therapeutic agents [129].

Clathrin-mediated endocytosis involves the uptake of extracellular molecules through invagination of the plasma membrane. The vesicles are formed when ligands interact with receptors on the plasma membrane, thus recruiting clathrin triskelions and adaptor proteins, which form a multifaceted cage structure [130]

Strategy		Mechanism	Examples	Ref.
Endosomal membrane destabilization	pH dependent	pH buffering (proton sponge effect)	Polyamines (PEI, PEAAc, Mglu-HPG)	[134]
		Pore-formation	Listeriolysin O (LLO) GALA peptide	[135]
	pH independent	Pore formation	Amphotericin B Melittin	[136, 137]
Fusion with endosomal membrane		Flip-flop mechanism	GALA peptide	[138, 139]
		Via viral fusion proteins/ peptides	HA2 fusion peptide/ hemagglutinin	[140]
Photochemical membrane rupture		Light-induced ROS and/ or heat generation	TatU1A-photosensitizer conjugates M-PLL (melanin-poly-L-lysine)	[141, 142]

Table 1.
Approaches for endosomal escape.

that is released inside the cell with the help of dynamin. These vesicles are known as clathrin-coated vesicles and can lose their clathrin coat and fuse with early endosomes (**Figure 4(1)**). They are directed towards degradation in lysosomes or recycled to the plasma membrane [131].

Extracellular cargo can also be internalized via clathrin- and caveolin-independent pathways (**Figure 4(3)**) [132].

Depending on the internalization mechanism, NPs have different fates. They can face lysosomal degradation when internalized through clathrin-mediated endocytosis while skipping this process when taken up through a caveolin-mediated mechanism [133].

Many nanomaterials are degraded in endocytic vesicles leading to new approaches of carrier designs that are able to escape the endosomal or lysosomal degradation. Three main strategies, presented in **Table 1**, are commonly used to bypass this cellular barrier for drug administration. They rely on molecules, which possess the ability to destabilize the endosomal membrane in a pH-dependent or independent way or to fuse with the endosomal membrane, leading to the release of previously internalized cargo. Another approach involves the photochemical membrane rupture via photothermal nanomaterials.

4. Diagnosis through molecular imaging mechanisms

Molecular imaging is a medical discipline related to medical imaging and is representing the evolution of imaging techniques for diagnosis and therapy monitoring. It involves cell biology and molecular biology [143].

Current clinical applications of molecular imaging are CT, SPECT, PET, MRI, US and also hybrid imaging techniques SPECT/CT, PET/CT or PET/MRI. CT, MRI and US provide anatomical information, while PET/CT, and SPECT/CT offer functional and molecular information [144]. All these techniques are based on the accumulation of a contrast agent at the target site [145].

Even if they provide high-resolution images from anatomical [146] to molecular level for further clinical investigations [147–153], there are some disadvantages regarding the use of them. High doses of radiation and exposure can cause DNA damage in some tissues [154, 155]. Also, radiopharmaceutical biodistribution and effectiveness may cause image artifacts and also side effects for the patient [156–159]. Moreover, the patient care quality is not granted in most of the cases [156].

4.1 NPs involved in diagnosis imaging strategies

Diagnostic imaging using NPs refers to the detection of specific disease sites through molecular recognition of tumor cell particularities like the overexpression of several genes and the presence of different cell surface molecules or media excreted compounds/molecules that are involved in various disease processes, microenvironment particularities and also cell development stages [160, 161].

Physical properties of nanoparticle systems are very important for molecular imaging applications. Nanoparticle accepted diameters for this application are between 30 and 150 nm. Usually, the nanoparticle surface is modified using a ligand in order to target specific tumor cell molecules. As more ligands are attached on the nanoparticle surface, there are more chances to bind the target cell. The amount of signaling groups influence the sensitivity of the detection method [145].

Some NPs have innate optical properties like QDs [162] and metallic NPs due to surface plasmon resonance [48, 163–165]. QDs nanoparticles labeled with ^{18}F-Fluoropropionate and functionalized with RGD peptides demonstrate proper optical characteristics for PET imaging of prostate cancer [166].

Gold nanoparticles proved long circulation time and useful optical properties like high spatial resolution and high sensitivity for CT imaging. By functionalization with chitosan polymers, they were used for colorectal adenocarcinoma imaging [167]. Also, they were conjugated with antibodies for lymph nodes and metastases imaging in squamous cell carcinoma, head and neck cancer [168]. Moreover, gold nanoparticles radiolabeled with ^{111}In and ^{125}I can be used in SPECT imaging of epidermoid carcinoma [169].

Iron oxide nanoparticles are widely used in MRI imaging because they can improve and enhance the contrast [170]. In glioblastoma, iron oxide nanoparticles functionalized with peptides and polymers accumulate within tumor microenvironment by forming self-assembly structures [171].

Furthermore, polymeric materials such as mesoporous silica nanoparticles carry tumor targeting properties and are proposed for PET imaging in breast cancer. Besides this, they are able to perform drug delivery applications [172].

Regarding US imaging, perfluorocarbon nanoparticles can be used for a real-time and non-invasive analysis of thyroid carcinoma [173].

Considering the other nanoparticle formulations (nanoliposomes, micelles, polymersomes, dendrimers and aptamers), these ones need to be functionalized with specific contrast agents and fluorophores. The advantages to implement NPs such as molecular imaging tools are biocompatibility and biodegradability [174], encapsulation properties [175], water solubility in some cases [176] and targeting ligands accessibility [177].

Fluorophores are widely used in diagnosis applications and imaging of cellular processes. One drawback of conventional fluorophores is represented by the loss of fluorescence after a long exposure to light, known as photobleaching.

Various processes are known to induce the molecular relaxation without the emission of light, which depends on different chemical or physical factors like temperature, pressure, the presence of organic molecules or polymers and ionic strength, resulting in a decrease in the fluorescence intensity, referred to

as quenching [178]. Quantifying this decrease in fluorescence emission can give information about the concentration of a specific compound in the proximity of the nano-objects. Lately, numerous diagnostic techniques based on this phenomenon have been introduced [179, 180].

On the other hand, another luminogen system based on a process called aggregation-induced emission (AIE), developed by Ben Zhong Tang's group in 2001 [181], gathered increased interest for imaging and theranostic applications. Most luminescent systems have a lower efficiency in an aggregated state, thus limiting the concentration that can be used for imaging purposes and at the same time the achievable intensity of the emitted light. However, in the case of AIEgens, aggregation works constructively becoming highly luminescent in concentrated solutions or in an aggregated state. The utilization of AIEgens in theranostics has lately become a reliable approach, because of several advantages that include good biocompatibility, excellent optical properties and simple preparation and conjugation [182]. One example implies the conjugation of an AIEgen (TPS) with a short peptide (DEVD) that is susceptible to caspase-3 cleavage and that is bound to a prodrug that induces apoptosis [183].

5. Targeted therapy

Targeted therapy is a form of treatment, which implies the ability of a drug to accumulate at a target site in the body and thus decrease the side effects in healthy cells and tissues. Nanocarriers are often used to improve the bioavailability of the active compounds at the target site and allow the use of significantly reduced concentrations, therefore limiting the exposure of normal cells to the toxic effects of the drugs [184].

The most common strategies for drug delivery include local drug delivery, passive targeting, physical targeting, magnetic targeting and active targeting [185].

Local drug delivery is a promising strategy for the treatment of metabolic disorders (diabetes and obesity) [186], periodontitis [187] and bone disorders [188] due to its potential to keep drug availability in the target site for a prolonged period of time.

Passive targeting is based on enhanced permeability and retention effect (EPR effect) present in many tissues [189, 190]. Macromolecules and NPs from the bloodstream accumulate preferentially in tumors and inflamed sites, where the permeability of the vasculature is often enhanced. Moreover, the lymphatic drainage system is damaged in tumors, leading to a prolonged retention of the macromolecules and NPs in the tumor interstitium [191].

Physical targeting depends on the optical, thermal and electrical properties of the carriers [192], which can disintegrate at lower pH values or higher temperature and release the free drug. The tumor microenvironment is more acidic compared to the normal surrounding tissues, due to the accumulation of lactate, and therefore provides an opportunity for the use of pH-sensitive nanocarriers in cancer therapy [193].

Another approach for drug targeting refers to the accumulation of superparamagnetic carriers in target sites under the action of external magnetic field. Thus, a larger dose of the drug can be released at the tumor site for an increased period of time and side effects of chemotherapy can be diminished [194]. Once systemically administered, besides the type and intensity of the magnetic field and size of the NPs, many biological factors influence the infiltration of the superparamagnetic carriers to the target site, including the effect of Brownian motion, blood viscosity, interaction of the particles with the red blood cells and blood matrix [195].

While in the case of passive targeting the physicochemical properties of the nanocarrier system play the major role, active targeting relies on the interaction between the surface of the carrier and antigens expressed on target cells. NPs are functionalized

Class	Ligand	Targeted biomarker	Disease (clinical trials = *)	Ref.
Antibodies	Trastuzumab, cetuximab, Anti-CD20 mAbs (Rituximab)	HER2 receptor, EGFR, CD20	Breast cancer*, esophageal carcinoma*, pancreatic adenocarcinoma*, head and neck cancer*, non-Hodgkin's lymphoma*, rheumatoid arthritis*	[197–203]
Peptides	Transferrin	Transferrin receptor	Cancer	[204, 205]
Small molecules	Folic acid	Folate receptor	Rheumatoid arthritis*, ovarian cancer, lung cancer*	[206, 207]
Aptamers	A10RNA, AS1411, Anti-MUC1	Extracellular domain of the PSMA, nucleolin, MUC1	Prostate cancer, breast cancer	[208–210]

**Refers to clinical studies.*

Table 2.
Commonly used molecules for active targeting.

by adsorption or chemical conjugation with a large variety of ligand types such as peptides, small molecules, proteins, and aptamers, which present a high specificity for epitopes or receptors that are uniquely expressed or overexpressed on the target sites [196]. Examples of commonly used ligands and their targets are presented in **Table 2**.

6. Theranostic NPs recently developed

Theranostics refers to the use of the nanoparticle for molecular imaging and therapy. Considering the biological barriers, the biocompatibility, easy surface modifications, controlled pharmacokinetics and biodistribution and accommodation in various microenvironment conditions are still necessary to be accomplished [211]. Polymers are widely used for NP formulations because of biocompatibility and biodegradability properties *in vivo* [212–215]. Besides coating the nanoparticle surface with polymers, the fluorophores and other contrast probes are widely used to achieve high-sensitivity molecular imaging.

There are three main theranostic directions that involve the use of nanoparticles. The first strategy refers to treatment effect evaluation through molecular imaging with NPs as contrast agents. The aim of the second one is to assess a nanoparticle therapeutic strategy with molecular imaging probes. The third one describes nanoparticles as target therapy agents and molecular imaging tools at the same time. In this regard, for the first two procedures, the NP system is either the evaluator or the evaluated component, and for the last strategy, these roles are overlapping. Each one of these roles makes possible the development of future therapies (**Figure 5**).

The nanoparticles' evaluator role (**Figure 5(1)**) can be emphasized in the next study. Zhang et al. developed Annexin A5-conjugated polymeric micelles with dual role: detection of apoptosis via SPECT and optical imaging and also therapy outcomes investigation. In this study, the apoptosis was induced by drugs like cyclophosphamide, etoposide, poly (L-glutamic acid)-paclitaxel and cetuximab (IMC-C225) anti-EGFR antibody. The NPs were used to observe the apoptosis-induced processes in lymphoma and breast cancer *in vivo*. Therefore, SPECT and fluorescence molecular tomography allowed cellular death visualization in tumors [216].

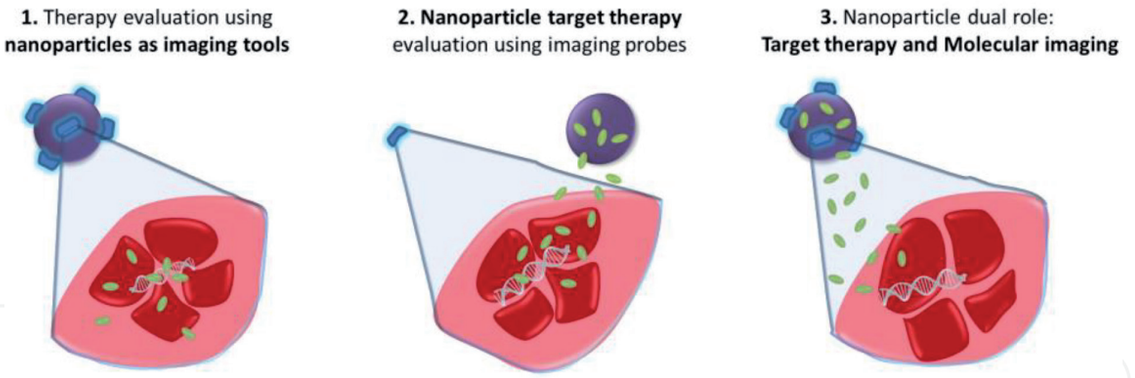

Figure 5.
Theranostic NPs action strategies.

NP effect evaluation (**Figure 5(2)**) can be performed based on probes that are currently used in clinical molecular imaging. For example, 2-deoxy-2-[F-18]fluoro-D-glucose (^{18}F-FDG) probe is used for metabolic activity measurements via PET/CT imaging. This radiolabeled probe can act as prognostic biomarker for nanoparticle-assisted photothermal therapy monitoring in neuroendocrine lung cancer *in vivo* [217].

Another strategy is to ensure both imaging and therapy at the same time (**Figure 5(3)**). In this situation, the nanosystem can be composed of two different components bonded together in order to perform a theranostic action.

The easiest way is to make use of the optical properties developed by some materials at nanoscale. Therefore, metallic nanoparticles can scatter and absorb the light in the NIR wavelength domain and are promising tools for cancer photothermal therapy [218].

In a different way, nanoparticles can be associated with molecular imaging techniques in order to enhance their efficiency. For example, doxorubicin-loaded polymeric micelles and perfluoropentane stabilized by the same block copolymer can perform US imaging and target therapy for breast and ovarian cancer [219, 220].

Some designs suggest the use of two different nanoparticles, which by conjugation with targeting ligands and drug molecules provide tumor visualization and target therapy. For example, quantum dot-mucin 1 aptamer-doxorubicin conjugates were used for ovarian cancer targeting and proved suitable optical properties for imaging and controlled release of the drug [221].

In addition to the molecular imaging techniques previously described, some nanoparticles can be used for photodynamic and photothermal therapy in order to perform targeting therapy.

Photodynamic therapy (PDT) implies the use of photosensitizer agents that under laser irradiation exert cytotoxic activity by generating reactive oxygen species [222, 223]. This therapy is very appreciated regarding multidrug resistance cancers and is suppose that it can replace the conventional chemotherapy [224]. PDT-specific nanoparticles are used as photosensitizer carriers [225, 226]. Moreover, these nanocarriers can be functionalized with targeting ligands for better tumor selectivity and also with drug molecules for therapeutic effectiveness [227–229]. Gold nanoparticles loaded with a fluorescent drug Pc4 targeting PSMA-1 membrane antigen in prostate cancer are promising tools for surgical guidance and further therapeutic intervention [228]. EGFR-targeted liposomal nanohybrid cerasomes are proposed for PDT and immunotherapy in colorectal cancer due to their sensitive detection properties and anti-tumor efficacy [229].

By a theranostic point of view, photothermal therapy (PTT), also known as hyperthermia or thermal ablation therapy, acts as a diagnosis and a treatment

Stage	Nanoparticle type	Therapeutic agent	Diagnostic agent	Pathology	Target	Ref.
Pre-clinical	Liposomes (100–200 nm)	Paclitaxel	pH-sensitive poly(ethylene oxide) (PEO)-modified poly(beta-amino ester) (PbAE) nanoparticles	Ovarian adenocarcinoma	EPR	[235]
	Silica (100–200 nm)	Paclitaxel and camptothecin	Superparamagnetic iron oxide nanocrystals	Pancreatic cancer	Folic acid	[236]
	Iron oxide (10–25 nm)	Anti-EGFRIgG	Iron oxide nanoparticles	Glioblastoma	EGFR	[237]
	Gold nanorod (10 x 40 nm)	Heat	Thermal/CT	Breast cancer	EPR	[238]
	Quantum dots (30–50 nm)	Paclitaxel, doxorubicin, 5-fluorouracil	Quantum dots	Many cancers	CD44, folic acid	[239]
Clinical trials	Silica (6–7 nm)	cRGDY	Ultrasmall inorganic hybrid nanoparticles	Melanoma and malignant brain tumors	$\alpha_v\beta_3$ integrin	[240]
	Cyclodextrin (70 nm)	RNAi	Transferrin	Solid tumors	Transferrin receptor	[241]
	Silica-gold nanoshell	Photothermal ablation	Nanoshell (MR and optical)	Head/neck cancer, primary and/or metastatic lung tumors	EPR	[242]
	Gold (27 nm)	Tumor necrosis factor alpha	Gold nanoparticles	Solid tumors	EPR (passive mechanism) rhTNF (active mechanism)	[243]
	Iron oxide	Endorem (superparamagnetic particles of iron oxide)	Iron oxide	Healthy volunteers	none	[244]

Abbreviations: EPR, enhanced permeability and retention effect; EGFR, epidermal growth factor receptor; cRGDY, peptide cyclo-(Arg-Gly-Asp-Tyr); rhTNF, recombinant human tumor necrosis factor alpha; RNAi, ribonucleic acid interference; MR, magnetic resolution.

Table 3.
Nanoparticles used in clinical (according to clinicaltrials.gov) and pre-clinical work.

strategy. It uses electromagnetic radiation in infrared (IR) region and provides high specificity analysis and minimal invasiveness [230]. The nanocarriers used for PTT need to have the capacity to target the tumor site after heat generation under laser irradiation [231]. For this purpose, various drug molecules and targeting ligands are encapsulated into nanoparticles. Gold nanoshells targeting HER2 positive breast cancer proved optical contrast and high tissue penetration under NIR irradiation [218]. Polymer nanoparticles functionalized with IR820 and doxorubicin were used in ovarian cancer and showed prolonged circulation time and drug accumulation at the target site [232]. It is important to mention that the generated temperature is usually between 42 and 45°C and sometimes higher depending on tumor tissue [233, 234].

6.1 Theranostic nanoparticles used in the clinic

There are various types of theranostic NPs that can be designed and used for cancer diagnosis and therapy. Their applicability is highlighted by liposomes, which are intensively used in clinical trials due to their specific features. In **Table 3**, several theranostic nanoparticles used in clinical (clinical trials) and pre-clinical work for cancer diagnosis and therapy are shown.

Theranostics has the potential to predict and evaluate therapy response, offering advantageous opportunities to modify the ongoing treatments and to develop new ones even in a personalized manner [245]. Nanoparticles have gained a lot of confidence in becoming important tools for a lot of medical applications due to their properties [17, 19].

The newest designs focus on hybrid nanostructures for better sensitivity and accuracy. These nanohybrids are currently studied and they proved effectiveness in cancer targeting by combining different imaging techniques with drug delivery strategies [246–248].

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Conflict of interest

The authors declare no conflict of interest.

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