Chapter 4
Cancer-Targeted Nanotheranostics: Recent Advances and Future Perspectives

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Introduction

Cancer represents a leading cause of morbidity and mortality at a global scale. Based on the WHO statistics, cancer is the cause of 9.6 million deaths in 2018, while approximately 17% of deaths is due to malignancies (World Health Organization, 2018). Even worse, new cases are expected to rise to 22 million by 2040 (Kohler et al., 2015). Thus, the need for the development of new methods for the efficient and personalized cancer management is of high priority.

During the past years, several potential applications of nanoparticles in the field of medicine have been studied thoroughly in critical areas that involve targeted drug delivery and medical imaging.

One of the most promising approaches is the combination of therapy and diagnosis (mostly refers to medical imaging) in a single platform (in the case of nanoparticles, it is referred to as a nanoplatform). These approaches resulted in the development of nanotheranostics which are expected to be important tools in the hands of clinicians. The need for such nanoplatforms is highlighted by the rapidly growing numbers of related publications (Viswanadh et al., 2018). Hopefully, these nanoplatforms will allow the monitoring of the disease (the extent of the affected tissues) and the visualization of the drug delivery kinetics, while the therapeutic efficacy will be increased.

In the current chapter, we present the most important concepts of nanotheranostics towards cancer management. In the first paragraphs, we discuss the most common forms of nanocarriers, and subsequently we examine their potential in therapeutic and imaging applications. Finally, the most novel nanoplatforms in

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clinical studies are described, while a discussion about translating nanotheranostics into clinical practice and their limitations is discussed at the end of the chapter.

Nanocarriers

Carriers (which due to their nanoscale size are referred to as nanocarriers) are a crucial element of every nanotheranostic system which aims to fuse therapeutic and imaging agents in a single platform (the terms nanoplatforms and nanocarriers are equivalent). Several types of nanomaterials have been studied for their potential uses in such platforms ranging from organic polymers to noble metal nanocarriers (Daglar et al., 2014; Fatima et al., 2020). Figure 4.1 shows some commonly used nanocarriers. In the following paragraphs, we will discuss the most promising carriers to date, liposomal, polymeric and inorganic nanocarriers.

Liposomal Nanocarriers

Phospholipids (and most importantly phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine) are the most aberrant components of any mammalian cellular membrane. Theoretically, any type of nanocarrier that would use these molecules would be expected to be highly biocompatible. Indeed, lipid nanoparticles of miscellaneous forms (such as micelles) have already been used in drug delivery systems. A typical example of the use of liposomal solutions in clinical practice is the use of doxorubicin (an anti-tumor agent) in the form of liposome injection (Access Data FDA, 2020). However, doxorubicin is not the sole drug that makes use of the unique opportunities that liposomal carriers offer. Several other drugs are

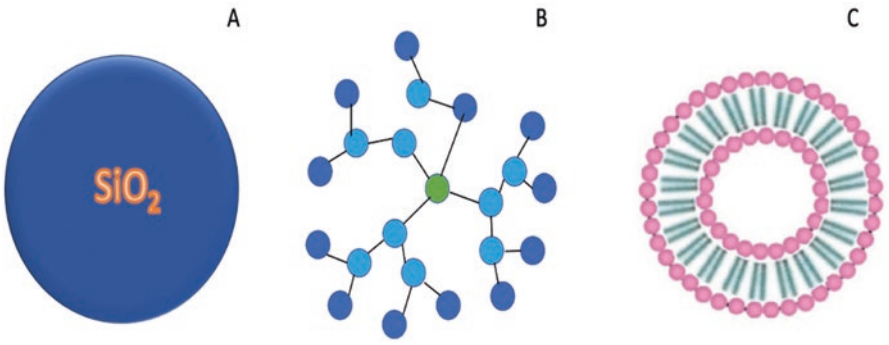

Fig. 4.1 Nanotheranostic platforms can use different types of nanoparticles that range from inorganic compounds such as SiO_2 (**a**) to organic compounds that include dendrimers (**b**) and liposomes (**c**). (Copyright Wiley-VCH GmbH. Reproduced with permission) (Ma et al., 2016)

already available for clinicians to prescribe, while the list of other liposomal-based drugs under clinical trials is constantly growing (Bulbake et al., 2017).

The liposomes used in these formulations can be of either natural origin or alternatively via chemical synthesis, while their size varies; some formulations are only a few nm in diameter, while others are more than an order of magnitude larger. When it comes to liposome formulation, a typical method is the rehydration of a lipid film followed by sonication (Luk et al., 2012). In order to form a theranostic nanocarrier, an additional step is required; an additional functional agent has to be loaded.

Due to the dual nature of a liposome (it contains a hydrophobic phase between the lipid layer and a hydrophilic aqueous core), they represent one of the most versatile "vehicles" for an agent to be attached. Whether hydrophilic or hydrophobic, many different agents in terms of chemistry and aqueous behaviour can be loaded. To date, many anti-tumor agents apart from doxorubicin have been successfully merged with nanocarriers in order to achieve a targeted release. Among these, cisplatin, one of the most efficient chemotherapeutic drugs and one of the most notorious for its side effects, has been added in liposomal formulations (Aldossary, 2019; Zahednezhad et al., 2020). However, the advantages of liposomes are not limited to their ability of loading both hydrophilic and hydrophobic agents. They also shield the loaded agents from the extracellular hostile environments that they face which results in prolonged circulation time and enhanced tumor accumulation which is boosted due to the enhanced permeability and retention effect (EPR Effect) (Golombek et al., 2018).

It should be noted that liposomes are not the only lipid-based nanocarriers available. Other formulations including oil-in-water emulsions that can encapsulate metal oxide nanoparticles (most notably iron oxides) and a dye (Cy7) that allows the monitoring of the effectiveness of a particular carrier are used in combination with the conventional MRI so as for medical imaging of increased clinical value to be obtained (Ma et al., 2016). Furthermore, solid nanolipids have been employed to deliver a combination of paclitaxel and a Bcl-2 targeting siRNA into cancer cells (Bae et al., 2013; Albuquerque et al., 2015).

Another advantage of using structures similar to these of a typical cell is immune clearance evasion. Membranes derived from red blood cells have been fused with polymer nanoparticles and have shown prolonged elimination half-life, a finding indicative of their possible anti-tumor potential (Hu et al., 2011).

Polymeric Nanocarriers

Polymeric nanoparticles represent a vast category of highly heterogeneous nanoparticles that include, among others, oligodendrimers, polymersomes and microbubbles. Their main purpose is to achieve a drug delivery technique with increased efficiency. A conjugation between a polymer and a chemotherapeutic drug (or any other type of drug) may augment the hydrodynamic size, decrease metabolic

clearance and at the same time provide a sufficient blood circulation half time. Combined, these parameters can improve the accumulation at tumor sites, while at the same time off-target effects could be reduced. The most commonly used polymers used in such conjugates are PEG and PLGA which have already met the approval criteria. The addition of an additional drug or imaging agent to increase the theranostic efficiency is currently a field of intense research (Ma et al., 2016).

Dendrimers represent a class of organic, intensely branched molecules with a dense exterior surface with several applications in medicine. When compared to standard polymers, these nanoparticles can form mono-dispersive nanostructures with abundant functional groups. Thus, theranostic agents can be bound via noncovalent bonds, while functional linkages permit responses triggered by different stimuli that can lead to the release of its cargo (in our case a chemotherapeutic drug).

Several dendrimer-based systems have been described in the field of cancer theranostics that include, among others, PPI (polypropylenimine) and PEG (polyethylene glycol) (Lo et al., 2013).

Shi et al. found that a dendrimer-based platform of generation 5-entrapped gold nanoparticle linked with a-tocopheryl succinate can increase CT imaging quality without reducing its therapeutic effects (Zhu et al., 2014).

Another type of polymers used in nanoplatforms is the amphiphilic block copolymers. These blocks contain a hydrophilic compartment (such as PEG) and a lipophilic compartment which triggers a controlled accumulation of these blocks due to hydrophobic interactions that occur inside an aqueous medium. Moreover, this block can be used to form structures of different shapes and sizes such as micelles and vesicles which are among the most useful structures that can serve the purposes of nanotheranostics. Such a structure has already been prepared by Liu et al. These structures are made from PEG-b-PKGA vesicles that have been loaded with doxorubicin and gadolinium that allow MR imaging while they show anti-cancer effects simultaneously (Liu et al., 2014b). A similar nanotheranostic approach was adopted by Chen et al. In this study, a chemotherapeutic compound and a fluorescent dye were engulfed in a polymeric micelle. This resulted in a nanotheranostic compound that allowed an image-guided anti-cancer treatment (Wan et al., 2014).

Despite the promising results of several self-assembled formulations, some major limitations are present. Most importantly, these structures may self-disassemble when the micelle concentration is not high enough. Another important issue is the maximum drug capacity that can be loaded in micelles. When approaches use both an imaging agent and a therapeutic one, the available space is limited. Thus, the anti-cancer drug load may be smaller to that of a micelle loaded only with an anti-cancer agent. A related issue is a possible mismatch between the fluorescent dye and the therapeutic agent that could disturb the desirable ratio among them, resulting in poor clinical outcomes.

Other possible candidates for theranostic applications are proteins. Their increased biocompatibility and their versatile nature that allows several modifications make them ideal molecules for such uses. Other advantages of proteins include their biodegradation and their non-immunogenic nature. By using a polypeptide that is composed of repetitions of a small peptide sequence, their assembly into

vesicles (or micelles) can be performed with increased precision. Zhu et al. (2015) used elastin-like polypeptides in order to build nanostructures (via self-assembly) that are stimuli-responsive. Interestingly, these formulations resulted in an almost full tumor regression.

Another example of the use of proteins is drug delivery systems based on albumin. Albumin is the most abundant protein in human plasma, and it is not surprising that it was one of the first proteins to be studied for such applications. An albumin-based system that aims to deliver paclitaxel (another chemotherapeutic agent) has already been approved by the FDA from 2005 (Mackay et al., 2009). Another abundant protein, apoferritin (which is ferritin without the Fe atoms) has also been used in nanoplatforms. Cutrin et al. (2013) encapsulated an MRI contrast agent and curcumin in apoferritin. The result was a nanocarrier which showed increased bioavailability, while the therapeutic effects of curcumin were preserved.

Practically, protein of any origin can be tested in nanocarrier formation. Indeed, nature has provided science several invaluable drugs and most notably antibiotics such as penicillin that allowed the treatment of the so-called white plague, tuberculosis (Barberis et al., 2017).

Thus, it is reasonable that several non-human proteins have been employed in nanocarrier formulations. For instance, gelatin has been widely used in nanocarriers. A 2019 study (Abdelrady et al., 2019) showed that gelatin nanocarriers were capable of delivering methotrexate during lung cancer therapy. The findings of this study were indicative of gelatin nanocarrier's potency; the IC50 of methotrexate was reduced to a fourth of that of methotrexate alone. A great advantage of gelatin is its abundant ionizable groups that allow the conjugation of several drugs or any other type of chemical modifications (Lohcharoenkal et al., 2014).

Another promising candidate is elastin. This protein is crucial for the connective tissue function as its name suggests it provides elasticity. A recent study (Dhandhukia et al., 2017) revealed that elastin-like nanocarriers were capable of suppressing tumor growth in a mouse model. This action was mediated by the encapsulation of rapamycin which resulted in superior tissue targeting.

Interestingly, researchers have moved even further from humans and animals, and plant proteins have also been tested recently. One of these is gliadin, a gluten protein that can be found in wheat and that has already been used in several pharmaceutical products (Arangoa et al., 2000). Its natural origin combined with its high biocompatibility and biodegradability has made it a potent tool in the field of nanophytotechnology. A recent study showed that anti-cancer drugs can be loaded into gliadin nanoparticles for the treatment of breast cancer (Gulfam et al., 2012), while its uses have been studied outside the field of oncology, even in the treatment of auto-immune diseases (Freitag et al., 2020).

Proteins found in milk may also be of use for such purposes. Two milk proteins b-lactoglobulin and casein have studied for their potential use as nanocarriers. The former has the characteristic of retaining its conformation even at acidic tissue environments while at the same time it can resist proteolytic processes (such as chymotryptic digestion). Its low cost combined with its abundance makes it a promising candidate for several drug delivery systems. A 2019 study (Bijari et al., 2019)

showed that irinotecan-loaded b-lactoglobulin nanoparticles had an increased effect on HT-29 cancer cells compared to the free drug.

Casein has also favourable physicochemical properties. It can withstand most processing treatments (heat and mechanical stress included), leaving its micelles intact. An in vivo study (Gao et al., 2019) showed prolonged survival times in mice that received casein nanoparticles loaded with 10-hydroxycamptothecin compared to the group that received 10-hydroxycamptothecin alone. At the same time, these nanocarriers managed to bypass the blood-brain barrier, which most of the time limits the therapeutic effect of conventional drugs. Thus, casein nanoparticles have a potential use for brain tumors and other brain pathologies.

Due to their abundance, soy proteins have been studied for several purposes in the field of medicine. Its balance between amino acids with different side chains (polar, non-polar and charged side chains) allows its conjugation with both hydrophilic and hydrophobic drugs. A 2019 study (Qian et al., 2019) employed phenylboronic acid in soy nanoparticles in order to make the tumor's environment. Indeed, these nanoparticles reduced the interstitial fluid pressure (which is increased in solid tumors due to blood vessel leakage and lymph vessel malformations). This finding is promising, since by reducing IFP, solid tumors could become sensitive to antitumor agents that otherwise could not penetrate the tumor cell (Heldin et al., 2004).

Inorganic Nanocarriers

Inorganic nanocarriers represent another wide category that includes several different nanomaterials with the potential use in theranostic nanosystems. Several metals including gold (Au) and platinum (Pt) as well as non-metals most notably silica (Si) have been tested the past decades to such uses (Lin et al., 2016).

Indeed, silica nanoparticles have been used in various forms that include, among others, mesoporous, solid and hollow nanoparticles. Additionally, the sol-gel preparation technique in SiO_2 nanoparticles allows the stabilization and the cross-linking between various therapeutic and diagnostic agents by forming a SiO_2 shell.

A 2020 study (Carniato et al., 2019) used a delivery system based on mesoporous Si that included rhodamine dyes, while the porous were impregnated with mitoxantrone (a chemotherapeutic agent). Interestingly, this nanotherapeutic system showed increased cytotoxicity on the MFC7 cells compared to the free drug, while medical imaging that was obtained (by using MRI scan) showed increased contrast enhancement when compared to untreated cells.

Another study (He et al., 2014) showed that mesoporous Si nanoparticles loaded with ruthenium polypyridyl complexes exhibit an increased cytotoxic effect on cancer cells via the induction of apoptotic pathways. The autofluorescence of the Ru complex served as an imaging agent making this formulation a promising theranostic nanocarrier.

Equally promising are the results of another type of non-metal nanocarriers, carbon-based platforms. These platforms are characterized by their high versatility

in terms of their possible formations. Fullerene nanoparticles (which are an allotrope of carbon and are composed of carbons linked with single and double bonds that form a mesh) are widely used in several biomedical applications (Lin & Lu, 2012). Their applications involve their use in cancer diagnostics (Sagman, 2002) and cancer treatment such as the targeting of cancer of melanoma. Their ability to bypass the BBB is also indicative of their potency as nanotheranostic carriers (Lin & Lu, 2012).

Carbon nanotubes are also valuable tools in cancer nanotheranostics. An easy way to visualize their shape is thinking of them as a graphene sheet that rolls up in many different ways forming the "nanotube". Their main classification refers to the number of layers that form the tube's walls. Thus, carbon nanotubes are categorized as either single-walled carbon nanotubes (SWCNTs) or multi-walled carbon nanotubes (MWCNTs) (Sanginario et al., 2017). CNTs can be loaded with anti-cancer agents which can be attached covalently or noncovalently. Noncovalent bond is important, since it has been suggested that any covalent modification of the therapeutic agent could decrease its anti-cancer potency. On the other hand, the weaker nature of noncovalent bond strength could decrease the attachment efficacy. Regarding the targeted drug delivery, a novel and promising approach includes the sealing of the nanotube's end with molecules that can be cleaved intracellularly. Thus, when the CNT has reached its destination (in this case the cancer cell), it can unload its cargo and selectively affects its target and no other tissue cells. Additionally, the CNT environment allows the attachment not only of drugs such as paclitaxel but also of small interfering RNA (Madani et al., 2011).

Graphene is another form of carbon that has been intensively studied the past few years. Its unique characteristics involve its particularly large surface area and the ease for cargoes to be loaded. Recently, Zhang et al. attached doxorubicin and Gd complexes to graphene oxide nanoparticles and showed their theranostic behaviour (Zhang et al., 2013).

Metallic nanoparticles represent perhaps the most important category of inorganic nanocarriers. Several different metals both noble and basic (and their alloys) have been tested with promising results. For instance, gold nanoparticles have been shown as potent contrast agents in X-ray scans and computed tomography (Mahan & Doiron, 2018). Similarly, Cu nanoparticles have been proved efficient for PET imaging applications (Lu et al., 2018). Recently, Han et al. (2019) showed that iron oxide nanoparticles (IONPs) can be used in dual modal imaging for the detection of breast cancer.

When compared to other nanoplatforms (regarding theranostic applications), metal nanoparticles have several important advantages. Firstly, their synthetic routes are well characterized, and practically metal nanoparticles can be formed in almost any desired shape and size (Abedini et al., 2016). Secondly, many metal NPs can serve as therapeutic agents on their own. For example, Ag NPs have been shown as promising anti-cancer agents in the literature (Raja et al., 2020). Thirdly, the versatile nature of metals allows their integration in structures of different metals that can have a synergistic effect. Lian et al. (2014) showed that IONPs engulfed in Au nanoshells can be used as MRI contrast agents and photothermal therapy (PTT). This

action was mediated due to a peak in the plasmonic resonance of the Au nano-shell in the near-infrared region.

The list of nanoparticles that can be used in theranostic nanocarriers is constantly growing in size as new materials are being tested. Semiconductor crystals, titanium dioxide nanoparticles (TiO_2 NPs) and metal organic frameworks (MOFs) have also been tested as promising candidates. MOFs are characterized by an excellent drug-loading capacity, bionic catalytic properties and satisfactory biocompatibility. Moreover, MOFs can be modified so as active targeting to be achieved via the use of ligands or the addition of antibodies (Cai et al., 2020).

All the aforementioned available materials for nanoplatforms make the whole process of selecting the most suitable nanocarrier a challenge. Moreover, among the myriad combinations between the different nanocarriers, therapeutic and diagnostic agents to make a selection of the most suitable make this challenge even greater. Important factors that will favour a nanocarrier over another include its maximum cargo loading capacity (in this case, a chemotherapeutic agent) and its release profile at tumour tissues. Additionally, the nanocarrier needs to be biocompatible; immune responses must not be triggered. The differences between the intensity of the EPR effect among different nanocarriers must be taken into serious consideration. The EPR effect refers to the selective accumulation of a substance at tumour tissue due to vessel malformation and poor lymphatic drainage (Patra et al., 2018). This effect represents a passive targeting approach that can result in a more efficient theranostic nanocarrier with less off-target effects. Another major limitation that may occur is possible alterations of physicochemical characteristics when switching from in vitro approaches to the bloodstream. Critical parameters include the nanoplatform's stability and its biological half-life. Finally, every nanocarrier with a potential of being translated into a clinical tool needs to be easily modified and to have an affordable production cost (Ma et al., 2016).

Anti-tumour Agents

Most conventional cancer therapies include chemotherapy, radiotherapy and surgery either alone or combined. However, each of them is tied with several side effects that severely affect a patient's life or worse; the possible side effects could exclude him from a potential therapy. Chemotherapy side effects may include thrombocytopenia and anaemia, cardiotoxicity, nausea and vomiting, among others (Oun et al., 2018). Radiation is associated too with several side effects. These include not only with the direct action of radiation (such as skin ulcers) but indirect effects as in the cases of head and neck cancer where it could lead to tooth decay and tooth loss because of the destruction of saliva glands (Mohan et al., 2019). Surgical approaches, apart from the risk that are associated with any surgical procedure, sometimes require patient rehabilitation and replacement of the lost tissues, since healthy tissue must also be removed in order to ensure no cancer cells were left behind (Benjamin, 2014).

Despite the serious side effects of any chemotherapy, its beneficial effects are considered greater, and this is the reason they are still used in clinical practice, since it increases the patient survival rates (Huang et al., 2017). The standard chemotherapy agent categorization includes different classes of chemotherapeutic drugs including alkylating agents (such as cisplatin), anti-metabolites (dehydrogenase inhibitors, nucleoside inhibitors, topoisomerase II inhibitors, kinase inhibitors) (Abotaleb et al., 2018), anti-tumor antibiotics (such as plicamycin) (Gao et al., 2020) and phytogenic anti-tumour agents. Figure 4.2 shows some common side effects of cisplatin as well as its chemical structure.

Unfortunately, despite the plethora of available cancer chemotherapy options, very few cancer nanomedicines have gained FDA approval. Indicative of the lack of such medicines is the publication of a review commenting exactly on the scarcity of nano-chemotherapeutic agents (Venditto & Szoka Jr, 2013). The first cancer nanodrug to be approved was Doxil (PEGylated liposomal doxorubicin) in 1995, followed by DaunoXome (liposomal daunorubicin). The past 5 years, five nanodrugs have been approved either in Europe or in the USA for cancer treatment: ONIVYDE (liposomal irinotecan), DHP107 (paclitaxel lipid nanoparticles), Vyxeos (liposomal daunorubicin combined with cytarabine), Apealea (a micellar form of paclitaxel) and Hensify (which is composed of hafnium oxide nanoparticles) (Salvioni et al., 2019).

A promising approach for incorporation with theranostic nanoplatforms is the use of prodrugs (precursor forms of drugs that are inactive). The use of prodrugs can be beneficial in terms of reducing the drug's toxicity other than the target tissues. For instance, Cao et al. used a cisplatin prodrug in a nanoparticle formulation (cationic lipid-assisted nanoparticles) in order to load greater amounts on the cancer cells and to counter tumour drug resistance (Cao et al., 2016).

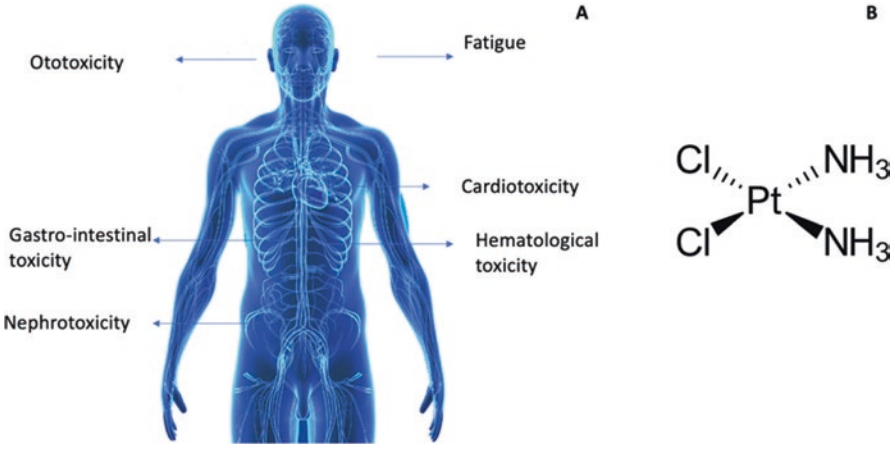

Fig. 4.2 Adverse effects of cisplatin (**a**) and the chemical structure of cisplatin (alkylating agent) (**b**)

A major goal of each delivery system is its ability to load and subsequently deliver a high drug amount at the desired target. However, an increased amount of drug may decrease its solubility in aqueous solvents. In order to avoid this issue, several nanosystems use platforms with a high surface-area-to-volume ratio or mesoporous formulations for use in theranostic approaches (Ma et al., 2016). Porous Si nanoparticles have been successfully integrated sorafenib (a kinase inhibitor) with a drug-loading percentage of approximately 28%, while the therapeutic agents can be released in a sustained fashion (Wang et al., 2015).

Another major barrier that cancer nanodrugs need to overcome is multidrug resistance (MDR) which is usually triggered by single-drug treatment protocols. A possible strategy to deal with this issue is the simultaneous administration of antitumor agents with P-glycoprotein inhibitors. Indeed, recent studies showed that this combination decreased cell viability compared to the use of the chemotherapeutic agent alone. Interestingly, the P-glycoprotein inhibitor when used alone did not provoke any decrease of cellular viability (Nanayakkara et al., 2018). Masking the charge of anti-tumour agents could also decrease MDR (Brigger et al., 2002).

A second commonly used approach is the simultaneous use of two different chemotherapeutic agents so as for synergistic effects to take action. However, this is no easy feat. Common issues that may occur during the combination of different drugs is the limited solubility of one or both drugs, limited permeation (which may result in a difference than the desired intracellular levels of both drugs) and even different drug stabilities (Jain & Thareja, 2019).

Nanoparticles in Medical Imaging

Imaging quality is a major characteristic of any theranostic nanosystem. Both preclinical and clinical trials involve computed tomography (CT), magnetic resonance imaging (MRI), ultrasounds (US) and positron emission tomography scan (PET scan) (Sanchez et al., 2013). All the aforementioned techniques are characterized by their excellent sensitivity and specificity making them reliable diagnostic methods that can be used during the initial diagnosis and during the monitoring of the disease (e.g. PET scan is a valuable technique to evaluate the effectiveness of a cancer treatment that involves surgical excision). Additionally, they can be used for the patient follow-up for the early detection of a possible metastatic site (Vensby et al., 2017).

Positron Emission Tomography

PET scan is an imaging technique commonly used during nuclear medicine applications. It is capable of providing 3D images that can be either static or dynamic (real-time imaging). Shortly, its principle of function includes the use of a nuclide that emits b+ radiation (positrons) which after a very short distance are annihilated via

the collision with an electron. Thus, two opposite photos occur and are subsequently detected by the imaging system. So far, the most commonly conventional PET radioisotopes include ^{11}C and ^{18}F (which can replace an H atom in a glucose molecule) (Ma et al., 2016; Vaquero & Kinahan, 2015). The complexation of the nuclide and the nanoparticle is an important aspect for the development of any radiotracer. The most common radiolabelling strategy involves the attachment of the radioactive metal to the nanosystem via chelators. Thus a "cold" nanoparticle is used, and the isotope is subsequently added, converting it into a "hot" nanoparticle. One of the most promising classes of radiolabelled theranostic nanoparticles, suitable for PET scan imaging, is silica nanoparticles. Their biocompatible nature and their well-defined chemistry make silica a promising candidate for the incorporation in PET scan imaging theranostic nanosystems. Ultrasmall silica NPs (with diameter of approximately 6 nm) have been approved by the US FDA while they have already been used for imaging in metastatic melanoma (Phillips et al., 2014; Goel et al., 2017).

Computed Tomography

CT imaging is an X-ray technique widely used in medicine that was developed more than half a century ago by Hounsefield and Cormack (Goodman, 2010). Currently, the clinically approved contrast agents that are used include small iodinated molecules and several barium (Ba) suspensions (Cormode et al., 2014). Unfortunately, these agents have been proved nephrotoxic in several cases, and thus renal function must always be checked. Thus, several patients may be excluded from the use of these agents and the increased imaging quality that this technique could offer (Andreucci et al., 2014). The fact that these agents are used in large doses due to their low X-ray absorption could also trigger hypersensitivity reactions (Ma et al., 2016). The basic principles of both PET scan and CT are shown in Fig. 4.3.

Nanotechnology research has focused on the development of several potential materials that could serve as CT contrast agents. Metals with high atomic numbers (Z greater than 50) are believed to be effective agents for CT imaging. A recent example is the research of Liu et al. who used PEGylated WO3-x nanoparticles for CT imaging applications merged with photothermal therapy. The formulation used showed no harmful effects upon normal tissue. On the contrary, tumour cells were ablated when exposed to near-infrared radiation (NIR) making this nanomaterial for nanotheranostic applications (Liu et al., 2014a).

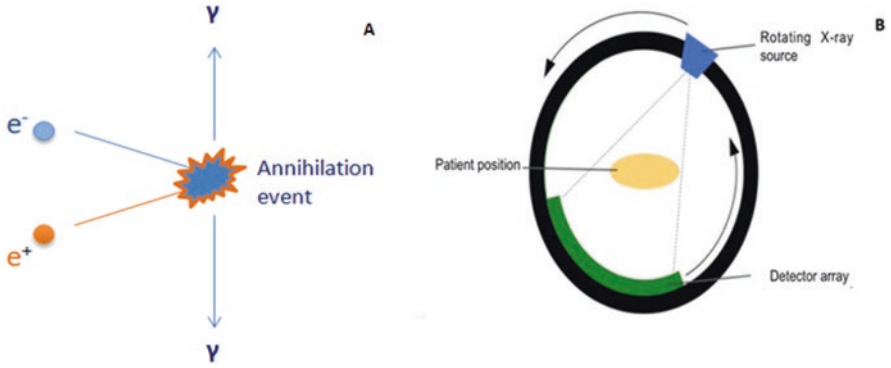

Fig. 4.3 The source of information during a PET scan derives from two opposite-direction photons that occur after an annihilation event between an electron and a positron (**a**). During a CT scan, the source of radiation is placed outside the patient, and the medical image is formed from the photons that reach the detector array (**b**). (Adapted from Open Access journal under the term of Creative Commons Creative Commons Attribution 4.0 License) (Cormode et al., 2014)

Nanotheranostics in Clinical Studies

The past 25 years, 50 different nanomedicines have received FDA approval and are currently used in clinical practice (Ventola, 2017). Most commonly approved formulations include polymeric, liposomal and nanocrystal nanodrugs, while drug delivery nanosystems based on NPs have been employed in approved nanodrugs including metal oxides and several other inorganic compounds (Ventola, 2017; Bobo et al., 2016). It is worth noting that a large percentage of the already approved nanodrugs are characterized by a reduced toxicity, while their efficacy is not heavily improved compared to standard formulations. Indeed, the main reason that several nanodrugs have failed clinical development is their inability to show a higher efficacy, since reduced toxicity can be already achieved by other drugs (conventional drugs and nanodrugs) (Caster et al., 2017). The basic characteristics of clinical trials (phase I and II) are shown in Fig. 4.4.

Nanoplatin (NC-6004, NanoCarrier Co., Ltd.) is a micellar formulation of cisplatin and is currently being investigated under phase 1 and phase 2 clinical trials either alone or combined with other chemotherapeutic agents such us gemcitabine. Another nanoformulation that is being tested is SN-38. Sn-38 is an active metabolite of a topoisomerase inhibitor (irinotecan). At least two phase 1 trials have been completed and a phase 2 trial in solid tumours (including breast cancer and non-small cell lung carcinoma, NSCLC). Additionally, Genexol PM (Samyang Biopharma) which is a micellar PEGylated formulation of paclitaxel is considered as an alternative to Kolliphor-based paclitaxel. This nanodrug has already been approved for use in patients with metastatic breast cancer in South Korea and currently is under phase 2 clinical trials in other countries.

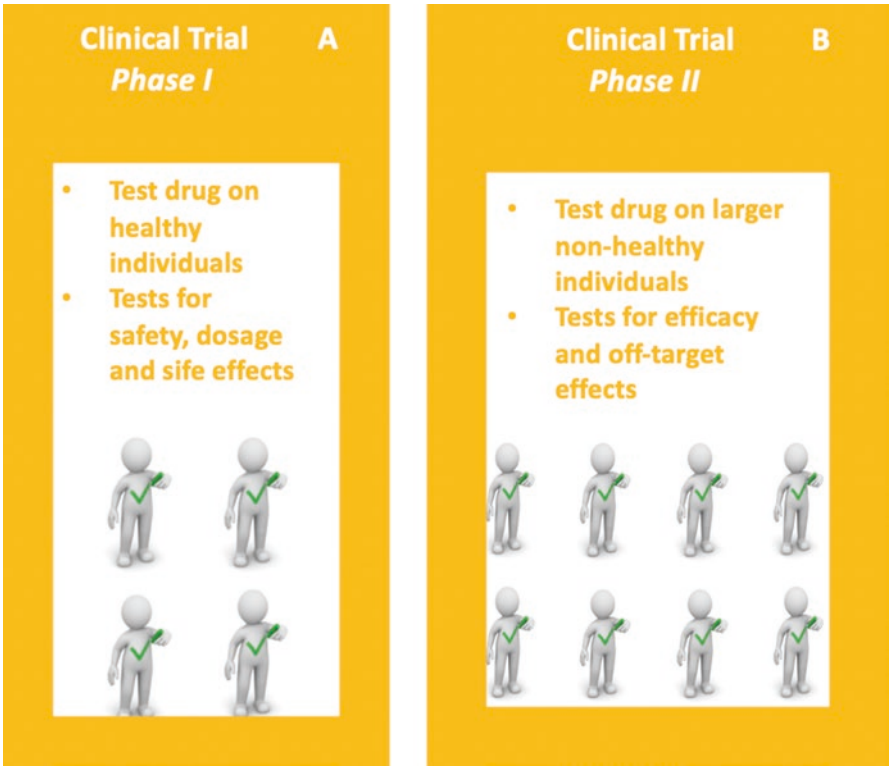

Fig. 4.4 The basic characteristics of phase I (**a**) and phase II (b) of a clinical trial

Cornell dots are capable of inducing cellular death and to reduce tumor size after several injections in treated mice. Their structure is based on an internal Si core which is labelled with a NIR dye, a targeting moiety and a polymer layer. This formulation results in a stable nanoparticle which is more than 20 times brighter than any conventional solution of the dye used. A human trial that involved five participants demonstrated a promising pharmacokinetic and safety profile when used as an imaging agent (Bobo et al., 2016).

Limitations and Future Perspectives

Although there are several research papers focusing on the benefits of several nanodrugs and nanoformulation for the treatment of cancer, there are several reasons that these agents fail to be translated into clinical practice. One of the most important limitations is the often-limited comprehension of interactions between biological components and the nanoparticle itself. Most importantly, the protein corona means that the nanoparticle's surface is covered with proteins which heavily alters its

stability, clearance and the possible immune response. The formulation of blood-like media is a promising effort that will allow the deeper understanding of this phenomenon. Regarding theranostic system, the control of the nanostructure's physicochemical properties is crucial. Usually, theranostic systems consist of an imaging and a therapeutic agent that work separately. Thus, accurate control is essential so as for the results of preclinical trials and in vitro research to be validated in clinical practice. An answer to that problem could be the development of smart theranostic systems. For instance, environmental stimuli that could include pH changes and enzymes at the target tissue could facilitate the accumulation or the activation of the nanoplatform. In order for this goal to be accomplished, the targeting agents and therapeutic agents could be designed so as to work synergistically and without negatively affecting the actions of one another.

Another important issue is the technical challenges that occur during productions. For example, in 2017, the production of DepoCyt was halted due to non-specified technical issues that affected its production (He et al., 2019; Pacira halts production of Depocyt, 2020).

Moreover, safety issues occur, despite the toxicity screening that each and every product under clinical trial has to face. Two examples are the MRX45 which failed at phase 1 since one out of five patients experienced serious adverse events from the immunity system and MM-3210 (2019) which also failed in phase 1 since it caused cumulative peripheral neuropathy (Mirna Therapeutics Halts Phase 1 Clinical Study of MRX34, 2020; Merrimack Discontinues Development of MM-310, 2020).

Another issue is the "controversial" EPR effect. While initially it was believed that the EPR effect was one of the greatest advantages of the use of nanoparticles that resulted in the tumor passive targeting (it has even been referred to as the golden principle), controversial statements are common in newer research papers. Such cases include the failure of the EPR effect in clinical studies or the presence of the EPR effect on mice but its absence on humans. An additional barrier is the poor pharmacokinetics that several nanoparticles show. The bloodstream levels of several nanoparticles draw rapidly due to the mononuclear phagocyte system. The speed of this process, which can range from minutes to hours, can affect the drug efficacy and can even lead to non-specific distribution of the nanoparticles to unwanted sites (Albanese et al., 2012). It should also be noted that despite the plethora of cancer animal models, their reliability at some cases is less than satisfactory. No known animal models can reproduce all the aspects of human disease (including cancer-driving mutations and the metastatic profile). This could be the reason that great differences occur in the therapeutic efficacy of a given drug between preclinical and clinical studies (Shi et al., 2017).

In summary, theranostic nanosystems are more than promising strategies that could bring precision medicine into clinical practice. There are several and important barriers in this field, but the intrinsic advantages of nanoparticles will sooner or later allow their extended use in clinical trials. For that purpose, the combined knowledge of researchers of different scientific backgrounds (chemistry and material science, biology and medicine) will ensure the know-how of building a

successful and at the same time smart nanosystem that its different parts (therapeutic and imaging agents) will work synergistically in order to provide maximum results.

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