Polymeric Nanoparticles for Drug Delivery

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The complexity of some diseases—as well as the inherent toxicity of certain drugs—has led to an increasing interest in the development and optimization of drug-delivery systems. Polymeric nanoparticles stand out as a key tool to improve drug bioavailability or specific delivery at the site of action. The versatility of polymers makes them potentially ideal for fulfilling the requirements of each particular drug-delivery system. In this review, a summary of the state-of-the-art panorama of polymeric nanoparticles as drug-delivery systems has been conducted, focusing mainly on those applications in which the corresponding disease involves an important morbidity, a considerable reduction in the life quality of patients—or even a high mortality. A revision of the use of polymeric nanoparticles for ocular drug delivery, for cancer diagnosis and treatment, as well as nutraceutical delivery, was carried out, and a short discussion about future prospects of these systems is included.

Keywords: nanoparticles ; nanocarriers ; polymeric materials ; drug-delivery systems ; ocular delivery ; cancer diagnosis ; cancer drug-delivery systems ; nutraceuticals

1. Introduction

The complexity of certain diseases and the toxicity associated with some treatments increasingly demand novel routes for drug delivery. A drug-delivery system (DDS) is a formulation or device that allows the introduction of active ingredients into the body in order to improve not only their efficacy, but also their safety, by controlling the drug amount, time and release in the site of action, crossing the biologic membranes to get to the therapeutic target [1]. This includes not only therapeutic drug administration methods, but also the use of vectors to facilitate their application and diffusion into the human body. In fact, different combinations of vectors and active ingredients may allow a wide range of possibilities for personalization, depending on particular diseases and patients. The routes used to administer and deliver active substances to their target tissue are a relevant factor when treating a disease [2]. These routes may have different effects depending on how they are applied. The administration is normally systemic. Occasionally, due to the severity of the disease or the toxicity inherent to the drug, it must be applied directly to the affected organ. Figure 1 shows the different anatomic routes of administration for drug delivery currently available. All delivery routes present inconveniences when delivering a formulation. As previously mentioned, the potential toxicity inherent to active ingredients or to the high dosage needed to achieve pharmacological effect, is a common disadvantage displayed by the systemic administration routes. The oral pathway of administration, for instance, limits the use of pH-resistant or highly hydrophilic drugs to ensure the required absorption by the intestinal epithelium cells. Likewise, the invasive nature of injections was associated with a high risk of infection.

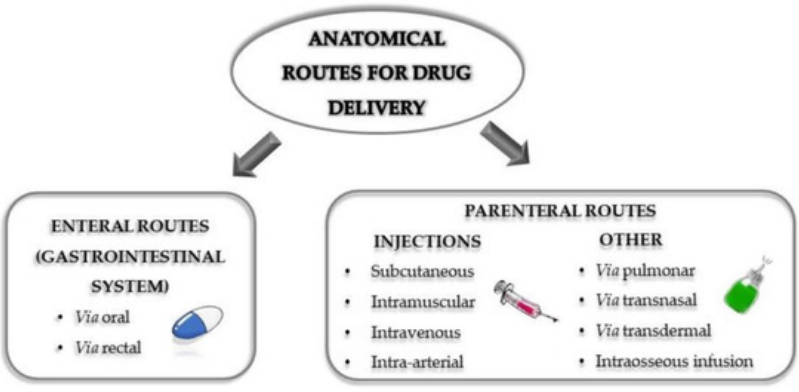

Figure 1. Classification of the different anatomic routes for drug delivery.

As stated above, to minimize the risks and disadvantages associated with traditional administration routes, DDSs are becoming increasingly more sophisticated [3], focusing on a better controlled release, maintaining therapeutic efficacy and the active ingredient targeting to the specific site of action, thus avoiding systemic release of the active substance. In this sense, nanotechnology is gaining high relevance, as it could potentially solve some of the issues associated with the above-mentioned traditional administration routes. The bioavailability refers to the portion of the bioactive compound absorbed in the body entering systemic circulation and performing functions. In general, nanoparticles (NPs) could be optimized to improve the drug bioavailability, either by increasing their absorption through enhanced solubility or by facilitating their passage through the biologic membranes [4]. Drug release could also be controlled and maintained at therapeutic levels, by adjusting the composition of the nanoparticulate system. They could even facilitate the combined therapy by the incorporation of more than one active ingredient. The progress in biologic therapies or immunotherapies has been promoted by the advances in nanotechnology, due to the fact that it allows a better administration of gen- or protein-based drugs. Functionalization of the NPs allows the recognition of the specific site of action, avoiding high systemic concentrations and reducing side effects. This property has been very useful in the diagnosis field by combining the specific targeting with the transport and release of a contrast agent [5].

According to the previously described characteristics of a nanoparticulate delivery structure, investigations about the use of different materials as nanocarrier precursors are an essential requirement for the improvement of the applicability and results achieved by these systems. These precursors should meet some requisites such as biocompatibility, biodegradability and non-immunogenicity [6]. Polymers are macromolecules formed by the covalent union of one or different sort of units, named monomers, to constitute a linear or branched chain. These monomers may possess any structure, as long as they have at least two functional groups where they can react with another monomer. Ideally, selecting the right kind of monomer/s, a polymer could be prepared to attain specific properties. Polymers are not only a special type of material that may encompass all the above-mentioned characteristics, but also, the great synthetic versatility they exhibit allows the researcher to customize them according to the requirements or final aims. In order to accomplish certain properties, polymeric tailoring could be carried out directly on biopolymers by chemical derivatization [7][8]. Another option is the preparation of synthetic polymers from their corresponding monomers which can lead to a large range of structures and applications [9][10][11][12]. These are the reasons why polymeric materials are gaining great relevance in nanotechnology in general and are being used as NP precursors for DDSs.

When considering the preparation of polymeric NPs, the use of surfactants may be a requirement. Surfactants are amphiphilic organic molecules that can self-assemble in solution. Most used surfactants are composed by a hydrocarbon chain (hydrophobic section) bound to an ionic functional group (forming the so-called cationic surfactants, such as benzalkonium chloride or tetramethylammonium hydroxide or anionic surfactants, like docusate or sodium laurate). Non-ionic surfactants can also be found, in which the amphiphilic character is generated by the union of hydrophobic and hydrophilic molecules (e.g., ethoxylated amines, alkyl and nonyl-phenol ethoxylates) [13]. Low molecular weight polymers could act as surfactants too, specially block copolymers (e.g., Pluronic F127 or Pluronic P123) [14]. In general, they are commonly included in the nanocarrier formulation as stabilizer agents and may be crucial to obtain a well-structured nanosystem, stabilizing the dispersion during nanoemulsion procedures. Some of the advantages of the stabilizers are to decrease the surface tension of NPs and increase affinity with lipidic structures [15]. Some surfactants have also demonstrated a significant reduction of the mean NPs diameter and also a double action as a cryoprotectant agent [16]. Studies of pharmacokinetics and biodistribution showed increased retention of the drug in the body and accumulation in the target tissue, prolonged time in the blood circulation along with a decreasing nephrotoxicity, hepatotoxicity, lower cardiovascular effects and reduced uptake of macrophage when surfactant surface-modified NP systems are used [17][18]. Multidrug resistance (MDR) mediated by the human ATP-binding Cassette (ABC) transporter superfamily such as *P*-glycoprotein (*P*-gp/ABCB1), multidrug resistance-associated protein 2 (MRP2/ABCC2) and breast cancer resistance protein (BCRP/ABCG2) have been recognized as the main obstacle against efficacy towards multiple chemotherapeutic agents [19]. Both organic and inorganic NPs have been demonstrated to inhibit the MDR. The effects of organic NPs are caused by several excipients, such as surfactants and polymers [20].

2. Polymeric Nanoparticles in Cancer Diagnosis and Imaging

According to the WHO, cancer is the second leading cause of death worldwide, with an estimated 9.6 million deaths in 2018. These data indicate cancer to be one of the diseases with the highest rate of morbidity and mortality nowadays. Finding effective methodologies for early detection, diagnosis and treatment has become a fundamental objective when developing NPs as DDSs [21][22][23]. Ordinary imaging and diagnosis techniques can only detect tumor mass when it is at least one-centimeter in size, being notably difficult to detect cancer at early stages [24]. This is the reason many researchers are currently trying to develop new and smaller composites able to identify malignant cells related to cancer

processes, in order to inform medical staff to devise a treatment strategy. Polymeric NPs have thus emerged as an alternative to limit ordinary contrast agents due to their surface modification abilities and their capacity to regulate solubility of the embedded agents in order to enhance imaging of cancerous cells. Some of the following recent investigations that have been consulted involve both therapeutic and diagnostic objectives (known as “theranostic agents”). This section of the review focuses on diagnostic and imaging results and just mentions some of the therapeutic facets.

2.1. Gold-Based Polymeric Nanoparticles Used in Cancer Diagnosis

Gold metallic NPs (AuNPs) and their derivatives are the most important investigation topic when describing new composites able to improve diagnosis and imaging techniques. Due to their versatility, they can be used in multiple imaging methods, providing high resolution and low or non-existent toxicity [25]. Computed tomography (CT) is one of the most commonly used diagnosis techniques in cancer imaging, mainly due to its low cost, high imaging resolution and compatibility with all types of patients. Scanning of soft tissues carried out by this technique requires contrast agents absorbing X-ray radiation. AuNPs have generated great interest as these agents, since they are nontoxic and present up to three-fold more efficiency in X-ray absorption than the current iodine-based CT contrasts agents. Other benefits related to AuNPs are the possibilities of designing and modifying their shape, size and surface. Although there are other NPs with a higher capability of X-ray radiation absorption, like bismuth-sulfide NPs, the control of their characteristics and the modification of their surface are more complicated [26][27]. In order to emphasize AuNPs contrast properties, encapsulation of these metallic NPs in polymeric NPs have been tested. Al Zaki et al. [28] designed and optimized polymeric micelles (AuMs) where 1.9-nm-size AuNPs were encapsulated within the hydrophobic core of micelles constructed from amphiphilic copolymer PEG–PCL. Blood pool contrast was obtained for 24 h and enhanced tumor margin delineation was observed, via CT, when AuMs were injected in living mice. Improvements in survival time when radiotherapy was applied were also demonstrated in these animals when treated with AuMs, compared to those which were not. Dedrimeric NPs were also investigated for the stable encapsulation of AuNPs for CT cancer diagnosis. Lin et al. [29] prepared a CD-derived 21-arm star-like triblock copolymer of β-CD-{PCL-poly(2-aminoethyl methacrylate)-poly[PEG methyl ether methacrylate]}. They combined a dendrimeric NP with the use of a CD unit in its nuclei, not only to stabilize AuNP as imaging agents, but also to embed doxorubicin to obtain a theranostic system. In vitro and in vivo experiments demonstrated the high-contrast properties of this system, characteristic of AuNP.

AuNPs can also be utilized in many other bioimaging techniques such as two-photon nonlinear microscopy, to study the binding coefficient between NPs and target cells and their absorption [30]. Single-photon excitation is a similar technique employed in vitro [31][32] to establish AuNPs accumulation in cells cytoplasm. Wang et al.[33] designed biodegradable polymeric NPs based on silica-coated AuNPs for photoacoustic imaging (PAI). This technique allows researchers to obtain images from biologic structures of different shapes and forms, even from organelles. It consists of the generation of wideband ultrasonic waves (called PA waves) due to thermoelastic expansion when a tissue is irradiated by near-infrared (NIR) light, which is absorbed by the target [34]. It is a very reliable technique to be linked to commonly used clinical diagnosing techniques. The gold nanospheres where synthesized, coated with silica, fluorinated and then introduced in a previously synthesized PLGA NP.

2.2. Gadolinium Polymeric Nanoparticles (GdNPs) Used in Cancer Diagnosis

Magnetic resonance imaging (MRI) allows three-dimensional high-resolution images to be obtained. It is useful for delimiting morphologic characteristics in tumors without producing ionizing radiation that could be harmful for the patient. This has become one of the best strategies in clinical cancer diagnosis [35]. To optimize this technique, contrast agents are utilized to enhance the variations between the different tissues, by lowering water relaxation parameter values (longitudinal or T1 and transverse or T2). There are many different types of contrast agents, but gadolinium-based materials are the most widely used [36] and mainly those formed by the chelated metal. While gadolinium-chelated complexes are easily eliminated from the organism by the kidneys because of their low molecular weight (<11 nm), if they are too big, they can be phagocytosed by macrophage cells (>200 nm) [37][38]. Nanotechnology has tried to overcome this inconvenience by designing new gadolinium-based contrast agents with enhanced imaging time, contrast effect and lowered toxicity, as well as granting passive targeting properties [39]. In order to modulate these characteristics, NP surface modification and full size control is necessary [40]. Some investigations have allowed enhancing of imaging by targeting key elements present in cancer cells, such as overexpressed surface proteins. To this end, Liu et al. [41] synthesized a novel multifunctional polymeric GdNPs-based contrast agent (Anti-VEGF PLA–PEG–PLL–GdNP). These nanoparticulate systems were designed with anti-VEGF antibody, which facilitates delivery to cancer cells in hepatocellular carcinoma (HCC) in order to improve its detection in early phases. Obtained NPs were 70–80 nm-sized, preventing them from being easily eliminated from the body. They managed to increase tumor area imaging time

significantly in comparison with control substances. In a different approach, polymerization-induced self-assembly (PISA), a synthesis method used in organic chemistry, was applied by Esser et al. [42] to obtain polymeric NPs including Gd ions. The corresponding amphiphilic triblock copolymer poly(glycidyl methacrylate)–block–poly(oligoethylene glycol methyl methacrylate)–block–polystyrene was prepared, which, after self-assembly into the corresponding NPs, was further functionalized with Gd^{3+} chelates. Depending on the polymer composition (proportion of each block), the NP shape and size could be modulated. MRI contrast efficiency was also characterized, compared and classified in terms of size and shape, demonstrating that filomicelles were the most promising candidates as MRI contrast agents.

Gadolinium has also been used as an imaging platform in PAI technique. The great depth penetration that NIR light reaches, makes NIR-light-absorbing materials (650–900 nm) such as organic materials, the ideal candidates for this technique [43][44], even if they are optically unstable. Gadolinium-based agents could overcome this issue, enhancing both imaging time and resolution. Developing polymeric GdNPs where Gd-complexes can be attached and immobilized in macromolecules [45][46][47], red blood cells [48], monoclonal antibodies [49], etc., is a tedious and complicated process. Hu et al. [50] detailed a synthesis pathway to obtain a poly(isobutylene-*alt*-maleic anhydride) (PMA) framework pendent with perylene-3,4,9,10-tetracarboxylic diimide derivatives and PEG, able to self-assemble by ultrasound, to which Gd^{3+} are easily attached. The optimal characteristics of these systems for being used in living organisms was demonstrated when they were injected into mice; excellent biocompatibility and photostability, good water solubility, low toxicity, strong PA signal intensity and a good performance as contrast agents and their ability to passively accumulate in tumors by enhanced permeability and retention effect. Photothermal in vivo treatment improvement was also observed, due to strong NIR optical absorbance and perfect tumor ablation properties, along with the absence of apparent toxic side effects in normal tissues. Wu et al. [51]also described GdNPs specifically designed for MRI/CT/PAI guided photothermal therapy, whose composition was Gd–PEG-coated Bi. These NPs absorb NIR light and transform it into heat, increasing the temperature to 40 °C and producing the in vivo tumor ablation as well as its eradication.

2.3. Perfluorocarbons Polymeric Nanoparticles (PFCNPs) Used in Cancer Diagnosis

Perfluorocarbons (PFCs) are molecules whose structure is similar to common organic compounds (e.g., alkanes). The difference between PFCs and regular organic compounds is that every hydrogen atom is replaced by fluorine (^{19}F) in PFCs, the most electronegative element in the Periodic Table. This exchange grants new and interesting properties that can be useful for medical applications. Nuclear magnetic resonance (NMR) is usually based on the ^{1}H signal from the water of the body's tissues and mobile hydrocarbon compounds. There are also other nuclei such as ^{19} F [52][53], which can be used in this technique to improve diagnosis and imaging effects. Unlike hydrogen atoms, most of the fluorine found naturally in the organism are located in bone structures, which as solid structures, restrict fluorine signal for MRI assays [54]. One of the major problems connected with the use of PFCs, is their solubility, due to the fact that they have high hydrophobicity. Research and development of new systems able to load contrast agents and enhance their biodistribution, has led to the design of nanoparticulate systems which raise their imaging effects. Kristen Wek [55]designed and characterized a polymeric NP containing fluorine compounds for enhanced NMR effect and passive targeting using a described copolymer [56], obtained from polyethylene glycol methyl ether methacrylate (PEGMEMA) and trifluoroethyl methacrylate (TFEMA) monomers with an azide functional group. NPs were synthesized through atom transfer radical polymerization (ATRP) in order to obtain a small polydispersity index and provide precise molecular weights and sizes. This system also showed passive diffusion into tumors and irrelevant ^{19}F NMR signal alteration. In a similar approach, Pisani et al. [57] synthesized polymeric nanoparticles containing liquid PFCs which were sensitive to ultrasound imaging. They synthesized a single core of liquid PFCs and a homogeneous PLGA–PVA polymeric shell, in order to increase the solubility using a variation of the regular emulsion-evaporation methodology. Perfluorooctyl bromide (PFOB), perfluorodecalin (PFD), and perfluorohexane (PFH) polymeric NPs were successfully synthesized and PFOB nanomaterials were characterized and described as nontoxic. In a posterior research work, Giraudeau et al. [58] carried out further investigations and compared these PFOB NPs with free PFOB in several assays, obtaining promising results. Surface functionalization is also used when synthesizing these NPs in order to achieve higher performance levels. Diou et al. [59] added RGD (arginine-glycine-aspartic acid) peptide, commonly considered for active tumor targeting, to the surface of PEGylated polyester nanocapsules of PFOB by pre- and post-functionalization strategies. They were tested in vivo in mice bearing CT26 tumors by ^{19}F MRI, showing very interesting results.

2.4. Other Nanoparticles Used in Cancer Diagnosis

Although the above-mentioned NPs are the most common nanoparticulate systems currently used for cancer diagnosis, there are others which are under investigation. These are mainly based on different absorbing compounds or on a synergistic union among techniques and/or contrast agents in one single NP. Liopo et al. [60] described the synthesis pathway and characterization of PEGylated biodegradable melanin-like nanoparticles (MNP–PEG) and their properties

used in photoacoustic tomography. MNP–PEG demonstrated biocompatibility with human MCF-7 and 3T3 cells and they remained stable in biologic medium for at least eight weeks. Belletti et al. [61]developed a synergy by joining two nanometric concepts, NPs and quantum dots (QDs). Their work was based on the concept that curcumin provokes apoptosis in primary effusion lymphoma (PEL) cells. However, this agent has a very low efficiency rate in this type of cancer treatment, due to its low solubility and consequently, low bioavailability. Encapsulating it in PLGA, NPs enhanced these characteristics and improved the amount of curcumin that was retained by the organism. QDs were also attached to the NPs surface as imaging agents, obtaining a theranostic application. The combination of two different metals in the particulate formulation was also explored. Another example was proposed by Zhou et al. [62] who combined Gd and Au advantages as contrast agents in MR and CT, respectively, to create new imaging agents for targeted dual mode tumor CT/MR imaging in vivo. In this research, PEI modified with folic acid and Gd chelators were used as a matrix to synthesize AuNPs. These systems were then complexed with Gd. Folic acid-targeted PEI-entrapped AuNPs loaded with Gd were characterized, showing good quality properties for in vivo applications: 3.0 nm size Au core, good water dispersion and nontoxicity. Regarding their imaging capabilities, a good X-ray absorption signal, higher than some other commercial contrast agents, and a reasonable r_1 relaxivity rate were shown, making them ideal candidates for dual mode nanoprobe use for targeted tumor CT/MR imaging in vivo. McQuade et al. [63] established a nanoplatform for theranostic purposes based on gold and superparamagnetic iron oxide NPs (SPIONPs) entrapped within a polymeric micelle, where amphiphilic diblock copolymer PEG–PCL acted as the polymer barrier in a similar assay as the aforementioned work by Al Zaki et al. [64]. On a higher level of complexity, Topete et al. [65] designed polymeric–gold nanohybrids to target multimodal theranostic agents, which are useful in optical and magnetic resonance. These folic acid-functionalized, doxorubicin/SPIONPs-loaded PLGA–Au porous shell NPs were tested in vitro in a human cervical cancer cell line in order to determine their physicochemical characteristics, cellular uptake and theranostic potential. They also reported an improvement in cellular uptake by applying an external magnetic field that guides the nanosystem to the cancer cells, as well as in targeting due to the folic acid.

Even though they are not considered strictly as polymeric nanoparticles, polymer-modified superparamagnetic iron oxide NPs (also called SPIONPs or Fe_3O_4 NPs) are remarkable contrast agents which are used in cancer imaging, thus deserving a special mention in this section [66][67][68]. Among their features, their capability to be surface-modified, in order to add polymeric agents that improve their imaging properties, as well as granting active targeting features, is a very powerful tool used in current investigations on developing new imaging agents [69][70][71][72].

3. Future Challenges in DDS

The application of nanomedicine represents a huge breakthrough in the above-mentioned fields and assures an encouraging advance in the next decade. Treatments will become more efficient and safer due to the enormous variety of NP design and functionalization. The lists of potential applications progress to the point where the nanocarrier can be customized to best adjust to a certain active ingredient, a specific environment and then provide fitting drug location at the site of action, in a controlled manner. However, it is relevant to mention that NP-based treatments are not perfect and have challenges to conquer. First, the number of polymeric materials currently available for their utilization as DDS is still limited although the R&D has been moved in the last decade, exceeding expectations, from the micro- to the nanosize scale. The ideal adjustment to the delivery conditions, such as transportation to the site of action, specific targeting or adequate delivery profile, among others, for each type of disease, requires the development of new polymers that can fit these requisites. Although selective targeting supposed a great improvement in comparison to non-encapsulated drugs, it is a very complex mechanism and represents a challenge itself. Overexpression of a specific surface protein is not enough to assure selective targeting as they are also normally expressed in normal cells. This point is more critical in cancer treatments , where administered drugs usually possess higher toxicity that could lead to numerous undesirable secondary effects compared to drugs used in other diseases treatments. Most the assays have been developed in small animal models showing promising results Figure 2, but the translation from animal results into clinical success has been limited. More clinical research and data are needed to fully comprehend the mechanism of these nanocarriers. In addition, limitations include the uncertain future of pharmaceutical companies which face high expenses concerning clinical trials and decreasing success rates in the flow of novel entities in the R&D pipeline. Examples of polymeric NPs that do not fulfil all the regulatory requirements for clinical evaluations and which had a harmful economic impact for their pharmaceutical companies are Livatag, PACA nanoparticulate formulation containing doxorubicin and BIND-014, PLGA polymer conjugated to docetaxel [73]. These formulations were potentially useful for the treatment of hepatocellular carcinoma and prostate cancer, respectively [73]. While BIND-014 began phase II of the clinical trial in 2018, the phase III studies of Livatag have not meet its primary endpoint of improving survival over, although it's action mechanism was demonstrated through DNA damage/synthesis inhibition and a decrease efflux pump by *P*-gp, due, at least in part, by an ion-pair association of doxorubicin with soluble degradation products of PACA which, conversely to free doxorubicin, are not a

substrate for *P*-gp [74]. However, in both cases, no improvement was found when evaluated [75][76][77]. Perhaps focusing on more specific diseases, also considering aging population, novel formulations or indications for previous blockbusters drugs, including polymeric NPs, could be a good recommendation to maintain a profitable economic growth rate. Achieving reasonable success for oral bioavailability of poorly absorbed lipophilic and hydrophobic drugs, to maintain adequate and effective plasma levels over prolonged periods of time, still remains an important challenge. In addition, the fact that drugs used for severe illness are usually administered only through the parenteral route and the inaccessibility of most pharmacological targets are major constraints that are increasing interest in developing more efficient nanodelivery systems. Conceiving new methods for the manufacture of NPs at reasonable costs is an important part of this challenge because there are only a small number of them that fulfill the appropriated requirements to reach the target and to subsequently deliver the drug in a suitable manner. It is also mandatory for these polymeric NPs to be biodegradable or to possess a high capacity to be eliminated outside the body avoiding accumulation, being nontoxic and non-immunogenic. It is remarkable to point out the role that copolymers could play in tuning or modulating the interactions with mucosa or blood proteins in order to control their in vivo fate or to stabilize NPs without the need of surfactants entities. It would be also interesting for the near future research in this field to include stimuli responding polymers which can confer triggered release properties. From a manufacturing point of view, nanospheres and nanocapsules could be easily obtained by applying the existing methods, but new structures like polymersomes, are still waiting for better synthesis to join the family of nanoparticulate DDS. The need for developing NPs with many capabilities (targeting, image contrast enhancement), named as multifunctional NPs, means more synthetical steps, more regulatory hurdles and higher expenses. Conquering these objectives may seem very difficult, but there is hope of reaching a better scenario.

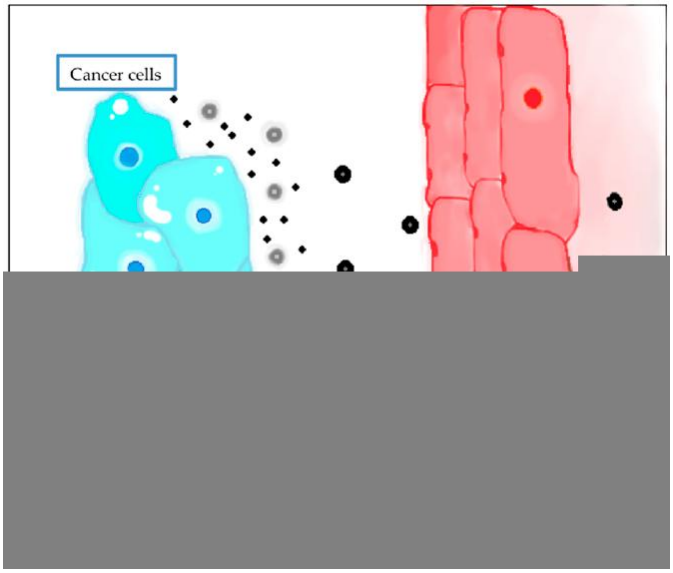

Figure 2. Schematic of the EPR effect: NPs pass through the endothelial fenestrations and reach cancer cells.

Over the last few years, there has been a global transformation in the field of nanomedicine, which has led to a multidisciplinary and collaborative approach with promising results and success. The future path of collaborations between theoretical and experimental scientists as well as the pharmaceutical industry, physicians and the regulatory agencies, will be crucial and will allow us to implement the laboratory results into the clinic and therefore, initiate the next generation of clinical therapies, trying to minimize the devastating consequences of terrible diseases such as pandemic covid-19.

In conclusion, many drawbacks or limitations still need to be resolved through numerous efforts and concentrated interdisciplinary scientific collaboration in order to reach the desired goals.

4. Conclusions

The toxicity associated with certain drugs and classical formulations or the complexity of treatment of some diseases, have driven the development of new alternatives as DDS. Among these, polymeric NPs are gaining high attention due to the biocompatibility, biodegradability and versatility they can offer, opening a wide range of materials that could possess the required characteristics for a specific application. For example, the use of hyaluronic acid in the NP outer surface increases adhesion to mucosal tissue and hence active ingredient liberation time, which is beneficial for drug delivery to eyes. Different techniques for cancer diagnosis are used with some disadvantages, such as the difficulty for early stage detection. The optimization of these techniques is possible due to different types of contrast agents, being NPs (e.g., gadolinium-based materials or AuNP) a promising agent in medical applications by the excellent biocompatibility, good water solubility and low toxicity. NP protection with PEG increases magnetic nanomaterials stability and avoids recognition

by macrophages, which increases circulation time, which is indeed a requirement for diagnosis. At the same time, given that ABC transporters mediated MDR is the main obstacle for effective cancer therapy, the use of PEG as coating material for polymeric NPs has recently been described as an effective tool for inhibiting ABC transporters. The simultaneous use of one single NP for both cancer detection and drug delivery makes NPs a potential theranostic. Regarding NP pathways for drug delivery, passive diffusion, active targeting as well as stimuli responsive systems have been described. In this respect, the functionalization of NPs with the precise antibody, improves recognition of the specific site of action to achieve therapeutic effect, which drastically reduces secondary effects of drugs for oncologic treatments. In addition, the inclusion of highly unstable compounds used as nutraceuticals inside PVs, prevents them from being exposed to environments that could affect their integrity, implying an improvement in their absorption by the gastrointestinal system and hence, an increment of their bioavailability. This would suggest a new approach in nanomedicine for the use of nutraceuticals as an alternative or complementary treatment for different pathologies. Although important progress has been made in the fields of ocular drug delivery, cancer diagnosis and treatment and nutraceutical delivery, areas of medicine with an associated high level of morbidity, a notable reduction in the patient's quality of life or even an important mortality, in most cases, the translation from animal tests to real clinical success has been limited. The efforts applied in the development of new polymeric materials that may encompass the specific requirements for a certain delivery system, the better knowledge the scientists have about disease mechanisms and the collaborative research work carried out among all scientific areas, will boost the current state of the use of NPs in the medical field, which will be translated into more efficient and safer treatments.

References

1. Bruschi, M.L.. Strategies to Modify the Drug Release from Pharmaceutical Systems; Woodhead: Cambridge, UK, 2015; pp. 87–194.
2. Jain, K.K.; An Overview of Drug Delivery Systems. *Methods Mol. Biol.* **2020**, *2059*, 1–54, https://doi.org/10.1007/978-1-4939-9798-5_1.
3. Macedo, A.S.; Castro, P.M.; Roque, L.; Thomé, N.G.; Reis, C.P.; Pintado, M.E.; Fonte, P.; Novel and revisited approaches in nanoparticle systems for buccal drug delivery. *J. Control. Release* **2020**, *320*, 125–141, https://doi.org/10.1016/j.jconrel.2020.01.006.
4. Jain, K.K.; Role of Nanobiotechnology in Drug Delivery. *Methods Mol. Biol.* **2020**, *2059*, 55–73, https://doi.org/10.1007/978-1-4939-9798-5_2.
5. Chen, Z.Y.; Wang, Y.X.; Lin, Y.; Zhang, J.S.; Yang, F.; Zhou, Q.L.; Liao, Y.Y.; Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. *Biomed Res. Int.* **2014**, *2014*, 1–12, https://doi.org/10.1155/2014/819324.
6. Essa, D.; Kondiah, P.P.D.; Choonara, Y.E.; Pillay, V.; The Design of Poly (lactide-co-glycolide) Nanocarriers for Medical Applications. *Front. Bioeng. Biotechnol.* **2020**, *8*, 48, https://doi.org/10.3389/fbioe.2020.00048.
7. Liu, R.; Zhao, J.; Han, Q.; Hu, X.; Wang, D.; Zhang, X.; Yang, P.; One-Step Assembly of a Biomimetic Biopolymer Coating for Particle Surface Engineering.. *Adv. Mater* **2018**, *30*, e1802851, https://doi.org/10.1002/adma.201802851.
8. Pla, D.; Gómez, M.; Metal and Metal Oxide Nanoparticles: A Lever for C–H Functionalization. *ACS Catal.* **2016**, *6*, 3537–3552, https://doi.org/10.1021/acscatal.6b00684.
9. Begines, B.; Zamora, F.; Violante de Paz, M.; Roe, I.; Mancera, M.; Galbis, J.A.; Synthesis and Characterization of New Carbohydrate-based Polyureas. *J. Renew. Mater.* **2013**, *1*, 212–221, .
10. He, Y.F.; Zhang, F.; Saleh, E.; Vaithilingam, J.; Aboulkhair, N.; Begines, B.; Tuck, C.J.; Hague, R.J.M.; Ashcroft, I.A.; Wildman, R.D.; et al. A Tripropylene Glycol Diacrylate-based Polymeric Support Ink for Material Jetting. *Addit. Manuf.* **2017**, *16*, 153–161, https://doi.org/10.1016/j.addma.2017.06.001.
11. Begines, B.; Zamora, F.; Violante de Paz, M.; Roe, I.; Mancera, M.; Galbis, J.A.; Synthesis and Characterization of New Carbohydrate-based Polyureas. *J. Renew. Mater* **2013**, *1*, 212–221, .
12. Begines, B.; Alcudia, A.; Aguilera-Velazquez, R.; Martinez, G.; He, Y.; Wildman, R.; Sayagues, M.J.; Jimenez-Ruiz, A.; Prado-Gotor, R.; Design of highly stabilized nanocomposite inks based on biodegradable polymer-matrix and gold nanoparticles for Inkjet Printing. *Sci. Rep.* **2019**, *9*, 16097, https://doi.org/10.1038/s41598-019-52314-2.
13. Nakama, Y.. Cosmetic Science and Technology. Theoretical Principles and Applications; Elsevier: Amsterdam, The Netherlands, 2017; pp. 231–244.
14. Zhao, T.; Elzatahry, A.; Li, X.; Zhao, D.; Single-micelle-directed synthesis of mesoporous materials. *Nat. Rev. Mater.* **2019**, *4*, 775–791, https://doi.org/10.1080/10837450.2017.1287731.

15. Belletti, D.; Grabrucker, A.M.; Pederzoli, F.; Menrath, I.; Cappello, V.; Vandelli, M.A.; Forni, F.; Tosi, G.; Ruozi, B.; Exploiting The Versatility of Cholesterol in Nanoparticles Formulation. *Int. J. Pharm.* **2016**, *511*, 331–340, https://doi.org/10.1016/j.ijpharm.2016.07.022.

16. Bonaccorso, A.; Musumeci, T.; Carbone, C.; Vicari, L.; Lauro, M.R.; Puglisi, G.; Revisiting the role of sucrose in PLGA-PEG nanocarrier for potential intranasal delivery. *Pharm. Dev. Technol.* **2018**, *23*, 265–274, https://doi.org/10.1080/10837450.2017.1287731.

17. Joseph, E.; Saha, R.N.; Investigations on pharmacokinetics and biodistribution of polymeric and solid lipid nanoparticulate systems of atypical antipsychotic drug: Eect of material used and surface modification. *Drug Dev. Ind. Pharm.* **2017**, *43*, 678–686, https://doi.org/10.1080/03639045.2016.1278014.

18. Gao, W.; Chen, Y.; Thompson, D.H.; Park, K.; Li, T.; Impact of surfactant treatment of paclitaxel nanocrystals on biodistribution and tumor accumulation in tumor-bearing mice. *J. Control. Release* **2016**, *237*, 168–176, https://doi.org/10.1016/j.jconrel.2016.07.015.

19. Chen, Z.; Shi, T.; Zhang, L.; Zhu, P.; Deng, M.; Huang, C.; Hu, T.; Jiang, L.; Li, J.; Mammalian drug eux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade. *Cancer Lett.* **2016**, *370*, 153–164, https://doi.org/10.1016/j.canlet.2015.10.010.

20. Yin, J.; Deng, X.; Zhang, J.; Lin, J.; Current Understanding of Interactions between Nanoparticles and ABC Transporters in Cancer Cells. *Curr. Med. Chem.* **2018**, *25*, 5930–5944, 10.2174/0929867325666180314122200.

21. Fathi Karkan, S.; Mohammadhosseini, M.; Panahi, Y.; Milani, M.; Zarghami, N.; Akbarzadeh, A.; Abasi, E.; Hosseini, A.; Davaran, S.; Magnetic nanoparticles in cancer diagnosis and treatment: A review. *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 1-5, https://doi.org/10.1016/j.cbpa.2018.04.014.

22. Zhou, X.Y.; Tay, Z.W.; Chandrasekharan, P.; Yu, E.Y.; Hensley, D.W.; Orendor, R.; Jeris, K.E.; Mai, D.; Zheng, B.; Goodwill, P.W.; et al. Magnetic particle imaging for radiation-free, sensitive and high-contrast vascular imaging and cell tracking.. *Curr. Opin. Chem. Biol.* **2018**, *45*, 131–138, https://doi.org/10.1016/j.cbpa.2018.04.014.

23. Wang, Y.; Xia, Y.; Optical, electrochemical and catalytic methods for in-vitro diagnosis using carbonaceous nanoparticles: A review.. *Microchim. Acta* **2019**, *186*, 50, https://doi.org/10.1007/s00604-018-3110-1.

24. Thakor, A.S.; Gambhir, S.S.; Nanooncology: The future of cancer diagnosis and therapy.. *CA Cancer J. Clin.* **2013**, *63*, 395–418, https://doi.org/10.3322/caac.21199.

25. Maham, M.M.; Doiron, A.L.; Gold Nanoparticles as X-Ray, CT, and Multimodal Imaging Contrast Agents: Formulation, Targeting, and Methodology. *J. Nanomater.* **2018**, *2018*, 5837276, .

26. Kim, D.; Park, S.; Lee, J.H.; Jeong, Y.Y.; Jon, S.; Antibiofouling Polymer-Coated Gold Nanoparticles as a Contrast Agent for in Vivo X-ray Computed Tomography Imaging. *J. Am. Chem. Soc.* **2007**, *129*, 7661–7665, https://doi.org/10.1021/ja071471p.

27. Rabin, O.; Manuel Perez, J.; Grimm, J.; Wojtkiewicz, G.; Weissleder, R.; An X-ray computed tomography imaging agent based on long-circulating bismuth sulphide nanoparticles. *Nat. Mater.* **2006**, *5*, 118–122, https://doi.org/10.1038/nmat1571.

28. Al Zaki, A.; Joh, D.; Cheng, Z.; De Barros, A.L.B.; Kao, G.; Dorsey, J.; Tsourkas, A.; Gold-Loaded Polymeric Micelles for Computed Tomography-Guided Radiation Therapy Treatment and Radiosensitization. *ACS Nano* **2014**, *8*, 104–112, https://doi.org/10.1021/nn405701q.

29. Lin, W.J.; Zhang, X.F.; Qian, L.; Yao, N.; Pan, Y.; Zhang, L.J.; Doxorubicin-Loaded Unimolecular Micelle-Stabilized Gold Nanoparticles as a Theranostic Nanoplatform for Tumor-Targeted Chemotherapy and Computed Tomography Imaging. *Biomacromolecules* **2017**, *18*, 3869–3880, https://doi.org/10.1021/acs.biomac.7b00810.

30. Park, J.H.; Park, J.; Kim, S.; Kim, S.-H.; Lee, T.G.; Lee, J.Y.; Wi, J.-S.; Characterization and application of porous gold nanoparticles as 2-photon luminescence imaging agents: 20-fold brighter than gold nanorods. *J. Biophotonics* **2018**, *11*, e201700174, https://doi.org/10.1002/jbio.201700174.

31. Fernández, T.D.; Pearson, J.R.; Leal, M.P.; Torres, M.J.; Blanca, M.; Mayorga, C.; Le Guével, X.; Intracellular accumulation and immunological properties of fluorescent gold nanoclusters in human dendritic cells. *Biomaterials* **2015**, *43*, 1–12, https://doi.org/10.1016/j.biomaterials.2014.11.045.

32. Wen, T.; He, Y.; Liu, X.-L.; Lin, M.-L.; Cheng, Y.; Zhao, J.; Gong, Q.; Xia, K.; Tan, P.-H.; Lu, G.; et al. Spectral shape of one-photon luminescence from single gold nanorods. *AIP Adv.* **2017**, *7*, 125106, https://doi.org/10.1063/1.5008544.

33. Wang, Y.; Strohm, E.M.; Sun, Y.; Wang, Z.; Zheng, Y.; Wang, Z.; Kolios, M.C.; Biodegradable polymeric nanoparticles containing gold nanoparticles and Paclitaxel for cancer imaging and drug delivery using photoacoustic methods. *Biomed. Opt. Express* **2016**, *7*, 4125–4138, https://doi.org/10.1364/BOE.7.004125.

34. Wang, L.; Hu, S.; Photoacoustic Tomography: In Vivo Imaging from Organelles to Organs. *Science* **2012**, *335*, 1458–1462, 10.1126/science.1216210.

35. Weissleder, R.; Molecular Imaging in Cancer. *Science* **2006**, *312*, 1168, 10.1126/science.1125949.

36. Caravan, P.; Strategies for increasing the sensitivity of gadolinium based MRI contrast agents. *Chem. Soc. Rev.* **2006**, *35*, 512–523, https://doi.org/10.1039/B510982P.

37. Chauhan, V.P.; Jain, R.K.; Strategies for advancing cancer nanomedicine. *Nat. Mater* **2013**, *12*, 958–962, https://doi.org/10.1038/nmat3792.

38. Choi, H.S.; Liu, W.; Liu, F.; Nasr, K.; Misra, P.; Bawendi, M.G.; Frangioni, J.V.; Design considerations for tumour-targeted nanoparticles. *Nat. Nanotechnol.* **2010**, *5*, 42–47, https://doi.org/10.1038/nnano.2009.314.

39. Ratzinger, G.; Agrawal, P.; Körner,W.; Lonkai, J.; Sanders, H.M.H.F.; Terreno, E.; Wirth, M.; Strijkers, G.J.; Nicolay, K.; Gabor, F.; et al. Surface modification of PLGA nanospheres with Gd-DTPA and Gd-DOTA for high-relaxivity MRI contrast agents. *Biomaterials* **2010**, *31*, 8716–8723, https://doi.org/10.1016/j.biomaterials.2010.07.095.

40. Caravan, P.; Zhang, Z.; Targeted MRI Contrast Agents. *Chem. Contrast Agents Med Magn. Reson. Imaging* **2013**, *1*, 311-342, https://doi.org/10.1002/9781118503652.ch7.

41. Liu, Y.; Chen, Z.; Liu, C.; Yu, D.; Lu, Z.; Zhang, N.; Gadolinium-loaded polymeric nanoparticles modified with Anti-VEGF as multifunctional MRI contrast agents for the diagnosis of liver cancer. *Biomaterials* **2011**, *32*, 5167–5176, https://doi.org/10.1016/j.biomaterials.2011.03.077.

42. Esser, L.; Truong, N.P.; Karagoz, B.; Moat, B.A.; Boyer, C.; Quinn, J.F.; Whittaker, M.R.; Davis, T.P.; Gadolinium-functionalized nanoparticles for application as magnetic resonance imaging contrast agents via polymerization-induced self-assembly. *Polym. Chem.* **2016**, *7*, 7325–7337, https://doi.org/10.1039/C6PY01797E.

43. Kim, C.; Song, K.H.; Gao, F.; Wang, L.V.; Sentinel lymph nodes and lymphatic vessels: Noninvasive dual-modality in vivo mapping by using indocyanine green in rats—Volumetric spectroscopic photoacoustic imaging and planar fluorescence imaging. *Radiology* **2010**, *255*, 442–450, https://doi.org/10.1148/radiol.10090281.

44. Song, K.H.; Stein, E.W.; Margenthaler, J.A.; Wang, L.V.; Noninvasive photoacoustic identification of sentinel lymph nodes containing methylene blue in vivo in a rat model. *J. Biomed. Opt.* **2008**, *13*, 054033, https://doi.org/10.1117/1.2976427.

45. Li, Y.; Beija, M.; Laurent, S.; Vander Elst, L.; Muller, R.; Duong, H.; Lowe, A.; Davis, T.; Boyer, C.; Macromolecular Ligands for Gadolinium MRI Contrast Agents. *Macromolecules* **2012**, *45*, 4196–4204, https://doi.org/10.1021/ma300521c.

46. Zhang, G.; Zhang, R.; Wen, X.; Li, L.; Li, C.; Micelles based on biodegradable poly (L-glutamic acid)-b-polylactide with paramagnetic Gd ions chelated to the shell layer as a potential nanoscale MRI-visible delivery system. *Biomacromolecules* **2008**, *9*, 36–42, https://doi.org/10.1021/bm700713p.

47. Hu, J.; Liu, T.; Zhang, G.; Jin, F.; Liu, S.; Synergistically Enhance Magnetic Resonance/Fluorescence Imaging Performance of Responsive Polymeric Nanoparticles under Mildly Acidic Biological Milieu. *Macromol. Rapid Commun.* **2013**, *34*, 749–758, https://doi.org/10.1002/marc.201200613.

48. Li, A.; Luehmann, H.P.; Sun, G.; Samarajeewa, S.; Zou, J.; Zhang, S.; Zhang, F.; Welch, M.J.; Liu, Y.; Wooley, K.L.; et al. Synthesis and In Vivo Pharmacokinetic Evaluation of Degradable Shell Cross-Linked Polymer Nanoparticles with Poly(carboxybetaine) versus Poly(ethylene glycol) Surface-Grafted Coatings. *ACS Nano* **2012**, *6*, 8970–8982, https://doi.org/10.1021/nn303030t.

49. Shahbazi-Gahrouei, D.; Williams, M.; Rizvi, S.; Allen, B.J.; In vivo studies of Gd-DTPA-monoclonal antibody and gd-porphyrins: Potential magnetic resonance imaging contrast agents for melanoma. *J. Magn. Reson. Imaging* **2001**, *14*, 169–174, https://doi.org/10.1002/jmri.1168.

50. Hu, X.; Lu, F.; Chen, L.; Tang, Y.; Hu, W.; Lu, X.; Ji, Y.; Yang, Z.; Zhang, W.; Yin, C.; et al. Perylene Diimide-Grafted Polymeric Nanoparticles Chelated with Gd3+ for Photoacoustic/T1-Weighted Magnetic Resonance Imaging-Guided Photothermal Therapy. *ACS Appl. Mater. Interfaces* **2017**, *9*, 30458–30469, https://doi.org/10.1021/acsami.7b09633.

51. Wu, B.; Lu, S.-T.; Yu, H.; Liao, R.-F.; Li, H.; Lucie Zafitatsimo, B.V.; Li,Y.-S.; Zhang,Y.; Zhu, X.-L.; Liu, H.-G.; et al. Gadolinium-chelate functionalized bismuth nanotheranostic agent for in vivo MRI/CT/PAI imaging-guided photothermal cancer therapy. *Biomaterials* **2018**, *159*, 37–47, https://doi.org/10.1016/j.biomaterials.2017.12.022.

52. Ruiz-Cabello, J.; Barnett, B.P.; Bottomley, P.A.; Bulte, J.W.M.; Fluorine (19F) MRS and MRI in biomedicine. *NMR Biomed.* **2011**, *24*, 114–129, https://doi.org/10.1002/nbm.1570.

53. Cyrus, T.; Winter, P.M.; Caruthers, S.D.; Wickline, S.A.; Lanza, G.M.; Magnetic resonance nanoparticles for cardiovascular molecular imaging and therapy. *Expert Rev. Cardiovasc. Ther.* **2005**, *3*, 705–715, https://doi.org/10.1586/14779072.3.4.705.

54. Knight, J.C.; Edwards, P.G.; Paisey, S.J.; Fluorinated contrast agents for magnetic resonance imaging; a review of recent developments. *RSC Adv.* **2011**, *1*, 1415–1425, https://doi.org/10.1039/C1RA00627D.

55. Wek, K.S. Development of Polymeric Therapeutic Nanoparticles: Toward Targeted Delivery and Effcient 19F MRI of Solid Tumors. Ph.D. Thesis, Case Western Reserve University, Cleveland, OH, USA, 2017.

56. Wallat, J.D.; Czapar, A.E.; Wang, C.; Wen, A.M.; Wek, K.S.; Yu, X.; Steinmetz, N.F.; Pokorski, J.K.; Optical and Magnetic Resonance Imaging Using Fluorous Colloidal Nanoparticles. *Biomacromolecules* **2017**, *18*, 103–112, https://doi.org/10.1021/acs.biomac.6b01389.

57. Pisani, E.; Tsapis, N.; Paris, J.; Nicolas, V.; Cattel, L.; Fattal, E.; Polymeric Nano/Microcapsules of Liquid Perfluorocarbons for Ultrasonic Imaging: Physical Characterization.. *Langmuir* **2006**, *22*, 4397–4402, https://doi.org/10.1021/la0601455.

58. Giraudeau, C.; Flament, J.; Marty, B.; Boumezbeur, F.; Mériaux, S.; Robic, C.; Port, M.; Tsapis, N.; Fattal, E.; Giacomini, E.; et al. A new paradigm for high-sensitivity 19F magnetic resonance imaging of perfluorooctylbromide. *Magn. Reson. Med.* **2010**, *63*, 1119–1124, https://doi.org/10.1002/mrm.22269.

59. Diou, O.; Fattal, E.; Delplace, V.; Mackiewicz, N.; Nicolas, J.; Mériaux, S.; Valette, J.; Robic, C.; Tsapis, N.; RGD decoration of PEGylated polyester nanocapsules of perfluorooctyl bromide for tumor imaging: Influence of pre or post-functionalization on capsule morphology. *Eur. J. Pharm. Biopharm.* **2014**, *87*, 170–177, https://doi.org/10.1016/j.ejpb.2013.12.003.

60. Liopo, A.; Su, R.; Oraevsky, A.A.; Melanin nanoparticles as a novel contrast agent for optoacoustic tomography. *Photoacoustics* **2015**, *3*, 35–43, https://doi.org/10.1016/j.pacs.2015.02.001.

61. Belletti, D.; Riva, G.; Luppi, M.; Tosi, G.; Forni, F.; Vandelli, M.; Pederzoli, F.; Anticancer drug-loaded quantum dots engineered polymeric nanoparticles: Diagnosis/therapy combined approach. *Eur. J. Pharm. Sci.* **2017**, *107*, 230-239, https://doi.org/10.1016/j.ejps.2017.07.020.

62. Zhou, B.; Xiong, Z.; Wang, P.; Peng, C.; Shen, M.; Mignani, S.; Majoral, J.-P.; Shi, X.; Targeted tumor dual mode CT/MR imaging using multifunctional polyethylenimine-entrapped gold nanoparticles loaded with gadolinium. *Drug Deliv.* **2018**, *25*, 178–186, https://doi.org/10.1080/10717544.2017.1422299.

63. McQuade, C.; Al Zaki, A.; Desai, Y.; Vido, M.; Sakhuja, T.; Cheng, Z.; Hickey, R.J.; Joh, D.; Park, S.-J.; Kao, G.; et al. Multifunctional Nanoplatform for Imaging, Radiotherapy, and the Prediction of Therapeutic Response. *Small* **2015**, *11*, 834–843, https://doi.org/10.1002/smll.201401927.

64. Al Zaki, A.; Joh, D.; Cheng, Z.; De Barros, A.L.B.; Kao, G.; Dorsey, J.; Tsourkas, A.; Gold-Loaded Polymeric Micelles for Computed Tomography-Guided Radiation Therapy Treatment and Radiosensitization.. *ACS Nano* **2014**, *8*, 104–112, https://doi.org/10.1021/nn405701q.

65. Topete, A.; Alatorre-Meda, M.; Villar-Alvarez, E.M.; Carregal-Romero, S.; Barbosa, S.; Parak,W.J.; Taboada, P.; Mosquera, V.; Polymeric-Gold Nanohybrids for Combined Imaging and Cancer Therapy. *Adv. Healthc. Mater.* **2014**, *3*, 1309–1325, https://doi.org/10.1002/adhm.201400023.

66. Sun, J.; Zhou, S.; Hou, P.; Yang, Y.; Weng, J.; Li, X.; Li, M.; Synthesis and characterization of biocompatible Fe3O4 nanoparticles. *J. Biomed. Mater. Res. Part A* **2007**, *80A*, 333–341, https://doi.org/10.1002/jbm.a.30909.

67. Qiao, R.; Yang, C.; Gao, M.; Superparamagnetic iron oxide nanoparticles: From preparations to in vivo MRI applications. *J. Mater. Chem.* **2009**, *19*, 6274–6293, https://doi.org/10.1039/B902394A.

68. Fang, C.; Zhang, M.; Multifunctional magnetic nanoparticles for medical imaging applications. *J. Mater. Chem.* **2009**, *19*, 6258–6266, https://doi.org/10.1039/B902182E.

69. Laurent, S.; Forge, D.; Port, M.; Roch, A.; Robic, C.; Vander Elst, L.; Muller, R.N.; Magnetic Iron Oxide Nanoparticles: Synthesis, Stabilization, Vectorization, Physicochemical Characterizations, and Biological Applications. *Chem. Rev.* **2008**, *108*, 2064–2110, https://doi.org/10.1021/cr068445e.

70. Zhao, C.; Song, X.; Jin,W.; Wu, F.; Zhang, Q.; Zhang, M.; Zhou, N.; Shen, J.; Image-guided cancer therapy using aptamer-functionalized cross-linked magnetic-responsive Fe3O4@carbon nanoparticles. *Anal. Chim. Acta* **2019**, *1056*, 108–116, https://doi.org/10.1016/j.aca.2018.12.045.

71. Luo, Y.; Yang, J.; Yan, Y.; Li, J.; Shen, M.; Zhang, G.; Mignani, S.; Shi, X.; RGD-functionalized ultrasmall iron oxide nanoparticles for targeted T1-weighted MR imaging of gliomas. *Nanoscale* **2015**, *7*, 14538–14546, https://doi.org/10.1039/C5NR04003E.

72. Pernia Leal, M.; Rivera-Fernández, S.; Franco, J.M.; Pozo, D.; de la Fuente, J.M.; García-Martín, M.L.; Long-circulating PEGylated manganese ferrite nanoparticles for MRI-based molecular imaging. *Nanoscale* **2015**, *7*, 2050–2059, https://doi.org/10.1039/C4NR05781C.

73. Alphandéry, E.; Grand-Dewyse, P.; Lefèvre, R.; Mandawala, C.; Durand-Dubief, M.; Cancer therapy using nanoformulated substances: Scientific, regulatory and financial aspects. *Expert Rev. Anticancer Ther.* **2015**, *15*, 1233–1255, https://doi.org/10.1586/14737140.2015.1086647.
74. Mura, S.; Fattal, E.; Nicolas, J.; From poly(alkyl cyanoacrylate) to squalene as core material for the design of nanomedicines. *J. Drug Target.* **2019**, *27*, 470–501, https://doi.org/10.1080/1061186X.2019.1579822.
75. Ledford, H.; Bankruptcy filing worries developers of nanoparticle cancer drugs. *Nature* **2016**, *533*, 304–305, 10.1038/533304a.
76. Onxeo's liver cancer drug Livatag fails in phase 3 trial . Pharmaceutical Business Review. Retrieved 2020-7-24
77. French Nanoparticle Therapy Fails to Improv Liver Cancer Treatment in Phase III . labiotech.eu. Retrieved 2020-7-24