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REVIEW ARTICLE

# Nanomedicine technology: current achievements and new trends

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**Abstract** Nanomedicines consist of biodegradable or biocompatible submicron-sized colloidal particles encapsulating a drug. Nanomedicine technology has emerged following pioneering work in the 1970s and has given rise to an enormous number of novel delivery systems and applications. Advances in chemistry and engineering have yielded a large panel of biocompatible and biodegradable materials from which nanomedicines can be made. We briefly review the main different types of existing nanomedicines, focusing particularly on those used in the clinic. We then examine the biological barriers nanomedicines must cross to reach their target after intravenous injection, and how these barriers can be overcome. Although mostly conceived for intravenous administration, nanomedicines hold potential for delivery by other routes, such as the oral, ocular and pulmonary routes, which we examine. Finally, we focus on new trends in nanomedicine technology such as stimuli-responsive nanomedicines and the combination of nanomedicines with imaging agents to yield the so-called nanotheranostics.

**Keywords** Nanomedicines · Drug delivery · Enhanced permeation and retention effect · Stimuli-responsive · Nanotheranostics

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## Introduction

Once classically administered, a drug is absorbed and then distributed into the different tissues of the organism, including the target/diseased tissue where it can exert its therapeutic activity. These steps are followed by metabolization, if any, and excretion. In most cases, the percentage of administered drug reaching the target tissue is rather low and side effects can be observed in other tissues. An ideal therapeutic agent, as postulated by Paul Ehrlich in 1906, is one that, like a "magic bullet" (*magische Kugel*), is able to reach, exclusively, its target. This concept was progressively applied by encapsulating drugs into increasingly complicated drug delivery systems, so as to increase the amount reaching the target. The main idea is to make drug fate dependent on the carrier in which it is encapsulated. Early work focused mainly on microcarriers, but submicronic carriers or nanocarriers offer additional advantages. Indeed, carriers ranging in size from tens of nanometers to a few hundred nanometers can be administered systemically (intravenously) or locally (eye, lungs, nose, etc.). In addition, a small size favors tissue and even intracellular diffusion, opening the way for molecular medicine. Over the past 40 years, investigation of the therapeutic abilities of drug-loaded nanocarriers has become a flourishing research field, leading to the emergence, as nanosized drug delivery systems reached the market, of the term nanomedicine.

Nanomedicines consist of biodegradable and/or biocompatible submicron-sized colloidal particles encapsulating a drug. Recent advances in formulation, material science and physical chemistry have led to the emergence of a broad range of nanomedicines of various sizes, architectures and surface properties and made from very diverse materials. In this short review, we first present the

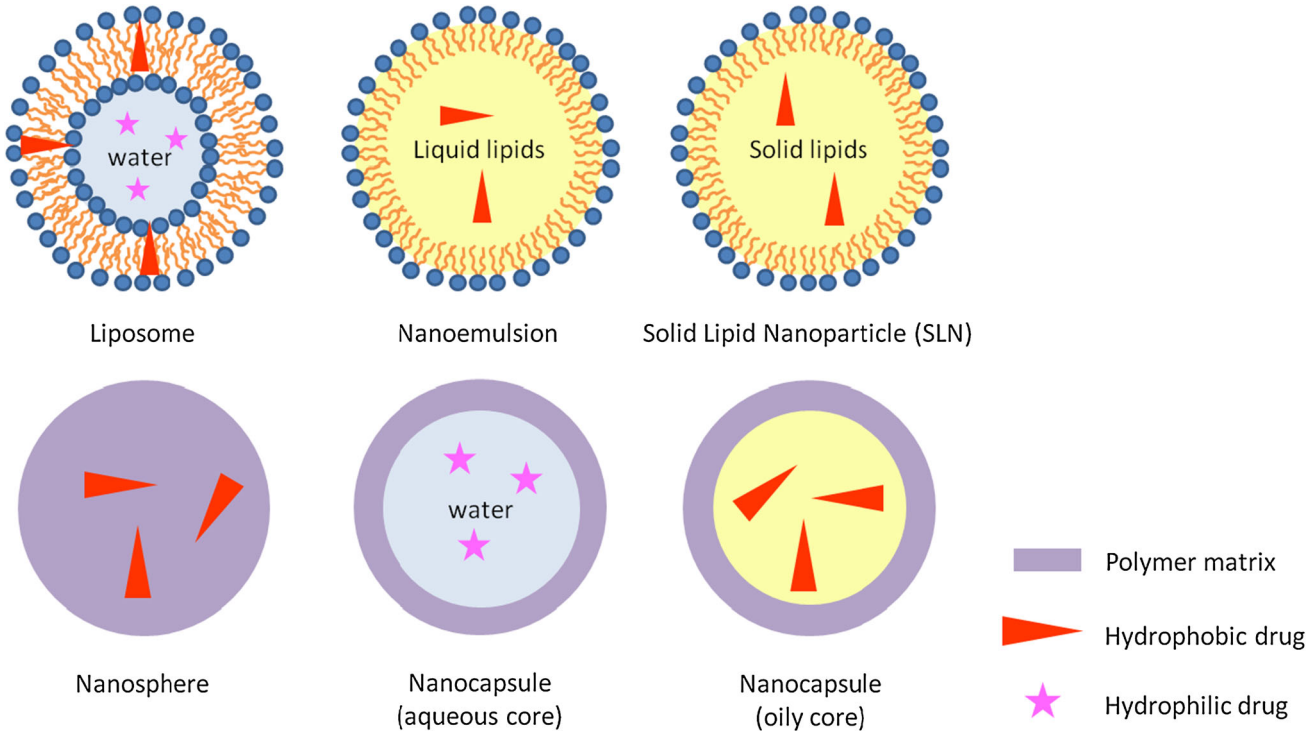


**Fig. 1** Schematic representation of different nanomedicines prepared using either lipids (*top*) or polymers (*bottom*) (color figure online)

different types of materials from which nanomedicines are made, before focusing on physiological barriers encountered by nanomedicines after their intravenous administration and how these barriers can be overcome. Alternative routes of administration are then presented, followed by new trends in nanomedicine technology: stimuli-responsive systems and nanotheranostics.

## Differents types of nanomedicines

The materials used to synthesize or formulate nanomedicines are extremely varied, ranging from organic molecules to inorganic ones. The very first nanomedicines were liposomes [1]. These consist of an aqueous suspension of vesicles, each comprising a bilayer composed of natural or synthetic phospholipids enclosing an internal aqueous compartment (Fig. 1). Their size can be adjusted by different methods such as extrusion or sonication. Drugs can be encapsulated either in the internal aqueous compartment, if they are hydrophilic such as doxorubicin [2] or 5-fluorouracil [3], or inserted within the bilayer if they are hydrophobic or amphiphilic such as amphotericin B [4]. The nature of phospholipids influences not only the encapsulation efficacy but also the in vivo fate of the liposomes after intravenous administration. Indeed, it has been shown that insertion of cholesterol in the bilayer makes it more rigid and, therefore, renders the liposome, if it is small enough (100–200 nm), more stable in the blood stream [5]. The development of liposomal formulations may be limited by the physical stability of the dispersions, drug leakage in the case of small molecules, low activity due to non-specific targeting, clearance by the mononuclear phagocytic system (MPS), and upscaling issues [6].

Other lipid-based nanosystems were considered for drug encapsulation. Lipid nanoemulsions consist of oily liquid lipid droplets, each surrounded by a layer of surfactant (Fig. 1). These droplets can encapsulate hydrophobic drugs in their liquid lipid core, provided the drugs are lipid soluble. They can also entrap amphiphilic molecules such as calixarene [7] or adsorb macromolecules such as antisense oligonucleotides by electrostatic interactions [8]. Their optical transparency, if droplet size is small enough, makes them suitable for topical ocular administration, for instance, to treat dry eye [9]. One disadvantage of nanoemulsions is their poor stability after intravenous injection. In addition, their production requires significant energy input and although low-energy methods exist, they are not yet ready for industrial-scale use. High concentrations of surfactants used to stabilize nanoemulsions may have deleterious effects [10].

Another example of lipid-based nanomedicine is that of solid lipid nanoparticles (SLNs) [11], which combine the advantages of other innovative carrier systems, such as

physical stability, protection of incorporated labile drugs from degradation, controlled release, and excellent tolerability, while also overcoming the time and in vivo stability issues of nanoemulsions. SLNs have a solid lipid core (i.e. solid at both room and body temperature) stabilized by a layer of surfactant (Fig. 1). The lipids used are mostly highly purified triglycerides, complex glyceride mixtures or even waxes. Although most SLNs contain hydrophobic drugs, methods based on solvent emulsification–evaporation for the preparation of SLNs loaded with hydrophilic drugs have been introduced [12].

Lipids have also been used, in particular cationic lipids, to formulate nucleic acids (DNA, siRNA, oligonucleotides) to yield nanomedicines [13, 14]. Cationic lipids, by means of electrostatic interactions, are able to condensate nucleic acids and form nano-objects able to protect nucleic acids from degradation and to favor their entrance into cells where they may exert their effect.

Historically, polymers are the second category of materials used to formulate nanomedicines. Polymer nanoparticles were first developed in the mid-1970s by Birrenbach and Speiser [15]. Later on, their application for the design of drug delivery systems became possible thanks to the availability of biodegradable polymers, considered to be suitable for human applications [16]. At that time, research on colloidal drug delivery was focusing only on liposomes but stable systems for clinical applications were lacking. Research has shown that nanoparticles could be more active than liposomes due to their better stability [17], allowing the encapsulation of many drugs (e.g.; antibiotics, cytostatics, nucleic acids). Many different polymers were synthesized and formulated to yield nanomedicines, including polyesters such as poly-DL-lactide, poly(lactide-co-glycolide) or poly-ε-caprolactone, poly-alkyl-cyanoacrylates and even polysaccharides.

These polymers can be formulated into nanospheres or nanocapsules depending on the process used for their preparation. Nanospheres are matrix systems in which the drug is dispersed throughout the whole matrix, whereas nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a single polymer membrane (Fig. 1). Several methods have been developed and can be classified into two main categories according to whether the preparation process requires a polymerization reaction or whether the preparation is achieved directly from a natural macromolecule or a preformed polymer. Nanoparticle preparation methods based on monomer polymerization generally consist of introducing a monomer into the dispersed phase of an emulsion, an inverse microemulsion, or dissolving the monomer in a non-solvent of the polymer. In these systems, polymerization reactions occur in two steps: a nucleation step followed by a growth step. For example, Couvreur et al. [16] developed nanospheres consisting of poly-alkyl-cyanoacrylates by anionic emulsion polymerization of alkylcyanoacrylate dispersed in an acidic aqueous phase. Two methodologies have been proposed for the preparation of nanoparticles from preformed synthetic polymers. The first involves emulsification of non-water-miscible organic solutions of preformed polymers into an aqueous phase containing surfactants, followed by removal of solvents under reduced pressure. Vanderhoff et al. [18] applied this method, named solvent emulsion-evaporation, to poly-DL-lactide. The solvent emulsion–evaporation process can also be modified to yield capsules with an oil or perfluorcarbon core surrounded by a polymer shell [19, 20]. The oil/perfluorcarbon is simply mixed in the organic solvent under the miscibility limit, along with the polymer. The rest of the process remains identical. To encapsulate hydrophilic drugs, a double emulsion (water-in-oil-in-water) is formed with the drug dissolved in the internal aqueous phase (Fig. 1). The second method for obtaining nanospheres from preformed polymers was proposed by Fessi et al. [21] and is called nanoprecipitation which is based on the precipitation of a polymer in solution following the addition of a non-solvent of the polymer. The solvent and the non-solvent of the polymer must be mutually miscible. The progressive addition of the polymer solution to the non-solvent generally leads to the formation of nanospheres around 200 nm in size. Surfactant may be used to promote nanosphere colloidal stability.

Polymeric micelles have also been proposed, deriving from the self-assembly in aqueous phase of amphiphilic copolymers, leading to rather spherical aggregates of a few nanometers in diameter [22]. Given that hydrophobic moieties organize as a core, they can encapsulate hydrophobic drugs thereby modifying their apparent solubility and thus their biodistribution. Amphiphilic copolymers can also form polymersomes, the polymer equivalent of liposomes: a bilayer of amphiphilic copolymer enclosing an internal aqueous compartment [23].

One limitation of classical nanomedicines is their rather low drug-loading capacity, usually below 10 % of the weight of the carrier itself. Researchers have overcome this drawback by synthesizing prodrug molecules that can self-assemble into nanomedicines. One of the best examples of this strategy is the squalenoylation concept. Squalenoylation consists of the formation of chemical linkage between a drug and squalenic acid, a natural precursor of cholesterol synthesis, followed by assembly of the new molecules into nanoparticles by nanoprecipitation [24]. Several molecules have been successfully coupled to squalene resulting in the formation of nanomedicines in which drug loading is increased to around 50 % of the carrier weight. Molecules covalently linked with squalene include gemcitabine [25], paclitaxel [26], siRNA [27] and nucleosides [28]. Studies

show a better efficacy of the prodrug nanoassemblies as compared with the free drug for tumor reduction [29].

Materials used are not limited to organic compounds and several groups have optimized inorganic nanomaterials to allow efficient encapsulation of active principles. Although metal organic frameworks (MOFs) were originally developed for hydrogen storage, it has recently been shown that these can be modified to yield nanosized MOFs that encapsulate drugs such as azidothymidine (AZT) or busulfan with rather high drug loadings [30]. Other groups have chemically linked drugs to iron nanoparticles [31].

## Crossing physiological barriers

Nanomedicines were mostly designed for intravenous delivery. According to their surface properties, they can be classified into three generations.

After intravenous injection, as non-self particles, nanomedicines are subjected to several physiological processes within the body. Their clearance or destruction may occur even before they are able to reach the targeted disease site. Understanding the role of physiological barriers is of the utmost importance to predict the fate of exogenous nanomedicines and their biodistribution.

Nanomedicines are usually prepared as colloidal suspensions in water or buffer solution. Stability can be assessed in different media to predict what may happen after intravenous administration [32]. In the vascular compartment, in the presence of salts, proteins and enzymes, aggregation, hydrolysis or cleavage of nanomedicines may occur. Nanomedicines below 10 nm are filtered out of the blood stream by rapid clearance through the glomerular capillaries of the kidneys. In the case of nanomedicines up to 500 nm, and depending on their surface properties (charges, hydrophilicity) and their shape, opsonization may occur, followed by macrophage uptake and segregation in organs such as the liver, spleen and bone marrow. Their preferred accumulation in macrophages was exploited to treat hepatocarcinomas with doxorubicin-loaded poly-alkyl-cyanoacrylate nanoparticles [33] or intracellular infections by delivering antibiotics to infected macrophages [34, 35].

Strategies to reduce nanomedicine opsonization led to the emergence of the second generation of nanomedicines characterized by passive targeting of solid tumors. To reduce opsonization, one can consider surface modification with either natural polymers such as polysaccharides (dextran, heparin, chitosan) [36, 37], or synthetic polymers such as polyethylene glycol (PEG) [38] (Fig. 2). The reduction of protein adsorption results in prolonged circulation of the nanomedicine in the blood compartment. Extending the plasmatic half-life increases the likelihood

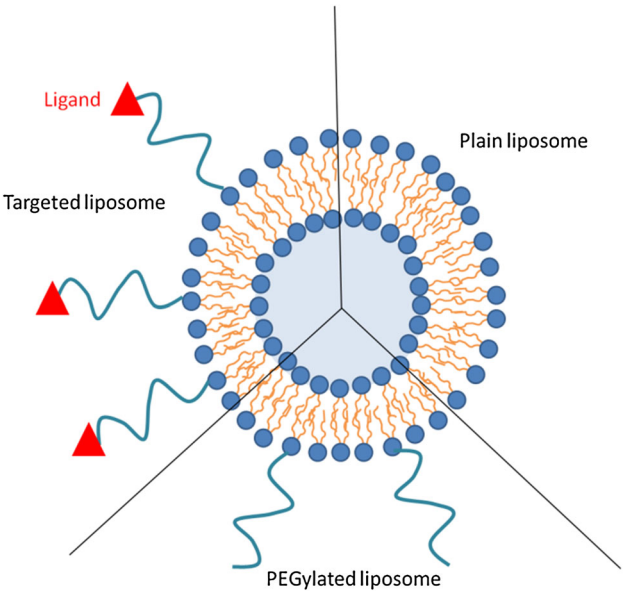


**Fig. 2** Schematic representation of the generation of the different liposomes: plain, PEGylated and targeted (color figure online)

of nanomedicines accumulating passively in solid tumors as a result of the enhanced permeation and retention (EPR) effect, which consists of escape through leaky vasculature and maximal retention due to reduced lymphatic drainage [39] (Fig. 3). The smaller the nanomedicines are, the more efficiently they extravasate through fenestrated neovessels. This property of PEGylated nanomedicine has led to the development of Doxil®/Caelyx®, one of the few nanomedicines used in the clinic. It consists of PEGylated liposomes, also called Stealth® liposomes, encapsulating doxorubicin, and it is used to treat cancer. Liposomal doxorubicin formulations favor a reduction of cardiac toxicity compared to free doxorubicin [40, 41]. Preclinical studies showed an enhanced antitumor activity for the PEGylated liposomal formulations compared with the free form [42, 43]. Clinical studies in patients receiving either PEGylated liposomal doxorubicin or equivalent doses of free drug have shown an up to 16-fold increase in doxorubicin levels in the tumor when using the liposomal formulation [2].

Passive targeting of tumors remains limited since the proportion of nanomedicines reaching the tumor site is usually below 10 % of the injected dose [44]. Moreover, as PEGylation reduces plasma protein adsorption, uptake by the reticuloendothelial system is also decreased. In addition, the degree of tumor vascularization and the porosity of the vessels depend on the tumor type and stage of development [45]. Finally, although observed in the clinic, the EPR effect seems to be limited to certain patients [46] and other strategies should be considered to increase

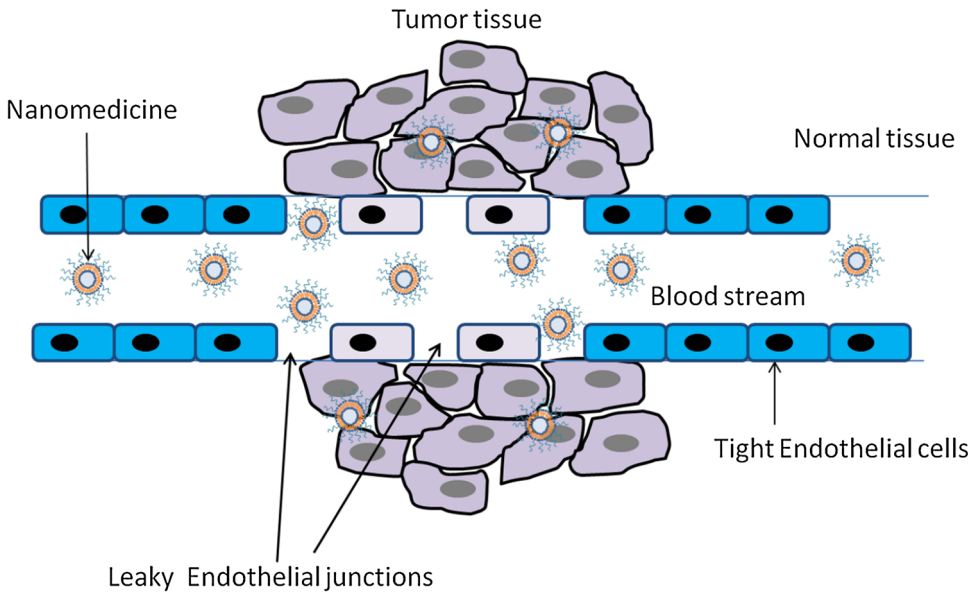


**Fig. 3** Schematic representation of ideal tumor passive targeting by long-circulating nanomedicines via the enhanced permeation and retention (EPR) effect (color figure online)

nanomedicine accumulation in solid tumors. In addition, it has been reported in several animals that intravenous injections of PEGylated liposomes may trigger an immune response leading to rapid clearance of PEGylated liposomes after a second injection [47]. Research is, therefore, focused on investigating several biopolymers such as polysaccharides to replace PEG in stealth formulations [14, 48].

The third generation of nanomedicines relies on active targeting. Active targeting overcomes the above-mentioned limitations by specifically attracting and/or binding nanomedicines to malignant tissues to increase local concentration. Active targeting can be obtained by applying an external force such as a magnetic field. Several authors explored the feasibility of using an external gradient magnetic field for solid tumor targeting with liposomes loaded with superparamagnetic iron oxide (SPIO) nanoparticles [49]. The magnet is usually placed over subcutaneously implanted tumors, with the magnetic field leading to enhanced accumulation of the nanomedicine in the tumors as compared with the EPR effect. This targeting strategy, however, remains difficult to translate to the clinic due to the need to implant a magnet near the tumor site.

Alternatively, there is the chemical approach of active targeting by decorating the nanomedicine surface with targeting ligands to promote receptor recognition (Fig. 2). Different ligands can be used: antibodies [50], peptides [51], proteins [52], aptamers [53] or small molecules such as folic acid [54]. Active targeting helps to avoid or reduce non-specific binding compared to ligand-receptor interactions. Usually a spacer is needed between the nanomedicine surface and the ligand to promote flexibility and accessibility. For this reason most groups attach the ligand at the extremity of the polymer coating the particle to protect it from opsonization. Active targeting allows increased cellular uptake of nanomedicines due to enhanced receptor-mediated endocytosis [55]. Active targeting is often based on a probabilistic hypothesis, namely that biomarkers such as integrins are overexpressed by endothelial cells on neovessels or epithelial cells. Jokerst et al. [56] considered that the differential of expression, between targeted and non-targeted tissues, of 2–10 was sufficient to ensure active targeting. Nevertheless, healthy tissues may be affected. The expression level of the biomarkers also varies with the genetic pool of the patient and the stage of the disease, therefore affecting the response to targeted nanomedicines. Instead of overexpressed receptors, exclusive receptors for malignant cells should, when possible, be considered. Glypican (GPC), which is absent in normal adult tissue but highly expressed (80 %) in hepatocellular carcinoma is a good example of such a strategy: Park et al. [57] highlighted the specific uptake by Hep G2 cancer cells using PEGylated particles coated with anti-GPC3 antibody.

## Beyond the intravenous route

Although nanomedicines are mainly designed for intravenous administration, many other routes of administration are being considered, such as the oral route, the pulmonary route and the ocular route. Of these, the oral route is the one usually preferred by the pharmaceutical industry for its ease of application. Indeed, nanomedicines can protect labile drugs from the degradation induced by the acidic

gastric pH. Insulin falls into this category. Although many nanomedicines encapsulating insulin for oral delivery have been developed and have shown promising results in animal models, none of them has yet reached the market, probably due to the narrow therapeutic window. Conversely, nanomedicine formulations may also protect the gastrointestinal tract from toxic or irritant drugs [58]. Some research has focused on the use of bioadhesive polymers for nanomedicine surface modification, the idea being to extend the residence time in the intestine and thereby favor drug absorption [59]. Bioadhesive polymers such as chitosan or thiolated chitosan are typical examples of this approach: their presence on the nanoparticle surface clearly enhanced the mucoadhesion behavior thanks to noncovalent interactions (ionic interactions and hydrogen bonds) with mucus chains. In addition, the presence of thiol groups, forming covalent bonds with the cysteine residues of the mucus glycoproteins, increased the mucoadhesion capacity [60].

Nanomedicines have also been developed for pulmonary delivery, either local delivery or systemic. Pulmonary delivery of nanomedicines, designed to target the highly vascularized alveoli, is a suitable alternative to the parenteral route since it allows the administration of fragile and poorly absorbed molecules [61, 62]. Nanoparticles are highly bioavailable after lung administration since they are well retained in situ and weakly taken up by alveolar macrophages, provided their diameter is below 250 nm [63]. Recent studies have demonstrated the impressive potential of biodegradable nanoparticles for the lung delivery of salbutamol [64]. Nanomedicine can be delivered to the lungs as an aqueous suspension by liquid nebulization [64] or as dry powders encapsulated into Trojan particles [65, 66] to be efficiently deposited deep in the lungs. Sung et al. [66] demonstrated that lung delivery of Trojan particles containing rifampicin allowed controlled release of this antitubercular drug and increased its bioavailability.

Nanomedicines have also proven their efficacy for ocular delivery by topical administration. Several nanomedicines with bioadhesive properties were developed to extend the residence time of the drug at the surface of the eye. In particular, cationic nanoemulsions developed by Novagali Pharma were successfully used for the treatment of the dry eye syndrome [9]. Intraocular injections of nanomedicines were also considered to target the posterior segment of the eye which, because of the hemato-aqueous and hemato-retinian barriers, is difficult to reach both by topical administration and by intravenous administration. For example, encapsulation of vasointestinal peptide into liposomes prevented its rapid degradation after intravitreal injection and extended its ability to downregulate uveitis for about 15 days [67].

## Stimuli-responsive nanomedicines

Traditional nanomedicines usually release their drug content by passive diffusion or by degradation of the material forming the nanomedicine (e.g. hydrolysis in the case of polyester nanoparticles). Recently, however, there have appeared stimuli-responsive nanomedicines, able to release their drug payload in a spatial, temporal, and dose-controlled fashion. The release process is complicated since it requires the use of biocompatible materials able to undergo a specific conformational change in response to the required stimulus or to take advantage of the properties of inorganic or organic materials when a specific physical stimulus is applied. Stimuli allowing control of drug release can be exogenous such as temperature, magnetic field, ultrasound waves, light or electric pulses, or endogenous such as pH, intracellular enzymes or redox gradients.

The concept of stimuli-responsive drug delivery was first proposed in the late 1970s using thermo-sensitive liposomes for the local release of drugs via hyperthermia [68]. The most frequently used stimulus for triggering drug release is temperature. Thermosensitive nanomedicines are designed to retain their drug load at body temperature ($\sim$37 °C) and specifically deliver the drug upon a slight temperature increase ($\sim$40–42 °C). Among the thermosensitive systems, one can cite polymeric micelles or nanoparticles based on poly(*N*-isopropyl acrylamide) (PNIPAM) which have a lower critical solution temperature [69]. Thermosensitive liposomes are also commonly based on fine-tuning of the lipid composition so that they exhibit a phase transition and conformational changes in the required temperature range. The temperature increase can be obtained using radiofrequency oscillations of a magnetic field or focused ultrasound waves. Doxorubicin-loaded thermosensitive liposomes (ThermoDox®, Celsion Corporation) are a typical example of thermosensitive nanomedicine currently being investigated clinically for different cancer treatments [70]. Perfluorocarbon nanoemulsions loaded with paclitaxel showed a substantial tumor regression and suppression of metastases upon ultrasound application [71]. Endogenous stimuli can also be exploited. For example, Castelleto et al. [72] designed a micellar carrier covalently linked to a drug moiety, whose release was induced by hydrolytic cleavage due to chymotrypsin in the extracellular enzymatic pool and acidic conditions of the tumor microenvironment.

## Nanotheranostics

One of the new trends in drug delivery concerns the association of a nanomedicine with a contrast agent to yield nanotheranostic systems allowing both imaging and

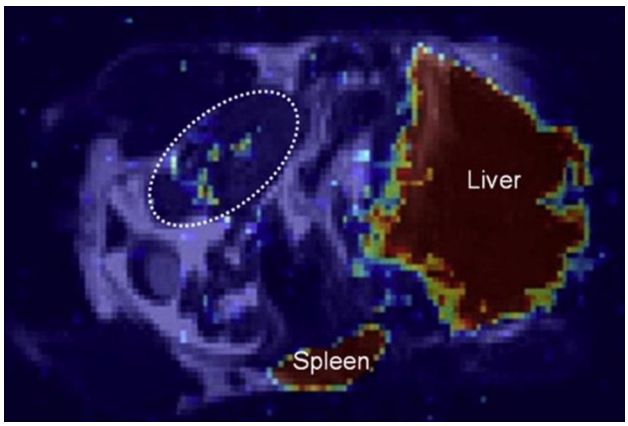


**Fig. 4** $^{19}F$ MR image superimposed with anatomical $^{1}H$ MR image of a tail-head longitudinal cross section of a mouse 7 h after intravenous injection of PLGA-PEG nanocapsules of perlfluorooctyl bromide for a tumor of 720 $mm^3$ (*white dotted circles*). Figures adapted from Diou et al. [44] (color figure online)

treatment. The term theranostic, deriving from the words therapy and diagnostics, was first used in 2002. Nanotheranostic systems are designed to image nanocarrier biodistribution, to survey the extent of disease, to deliver treatment and to monitor in real time its mechanism of action and its efficacy [73]. In brief, nanotheranostic systems make it possible to "administer the right drug to the right patient at the right moment" [74]. The carrier should provide an optimal biodistribution and should deliver two payloads: the imaging probe (metallic nanoparticles, quantum dots, fluorophores, etc.) and the bioactive molecule (peptide, protein, nucleic acid or chemotherapeutic drug). The numerous possible combinations of these three elements, their synthesis and their features have already been widely reviewed [75, 76].

Magnetic resonance imaging (MRI) is often chosen as the imaging modality since it provides good resolution and can cover most organs, including the brain. In addition,

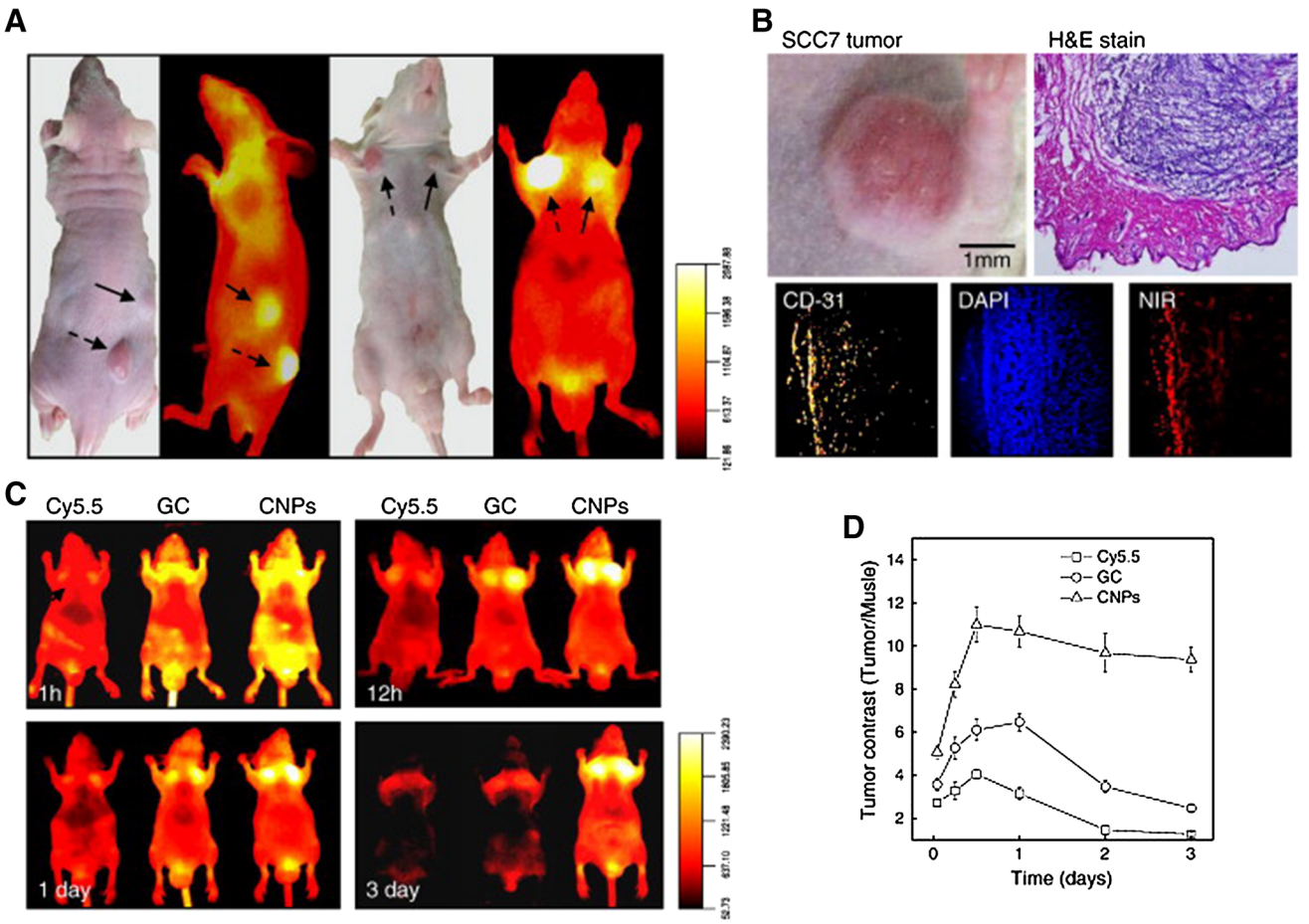


**Fig. 5** **a** In vivo imaging of Cy5.5-labeled chitosan-based nanoparticles (CNPs) in tumor-bearing mice. **b** The pectoral tumor was positive for tumor cells, as confirmed by H&E staining. Fluorescence microscopic images show the CD-31-positive angiogenic vessels (*yellow*) and DAPI-stained tumor cells (*blue*). Intravenously injected, Cy5.5-labeled CNPs were visualized in tumor tissues (*red*). **c** Time-dependent tumor targeting specificity of free Cy5.5, Cy5.5-labeled polymers, and Cy5.5-labeled CNPs, all with equimolar amounts of Cy5.5 (0.16 μmol). **d** Tumor-to-background (muscle) ratio as a function of time after administration of Cy5.5, Cy5.5-labeled polymers, and Cy5.5-labeled CNPs. All data represent mean ± SE. Adapted from Kim et al. [83]. (color figure online)

many MRI contrast agents have been developed that can easily be co-encapsulated into nanomedicines: Gd chelates, superparamagnetic iron oxides (SPIOs), ultrasmall superparamagnetic iron oxides (USPIOs) [77], perfluorocarbons (Fig. 4) [44, 78]. Viglianti et al. performed a meticulous analysis of the release of doxorubicin from liposomes, co-encapsulated with manganese as the MRI contrast agent. They linearly correlated the increase of longitudinal relaxivity (r1) by MR spectroscopy with the doxorubicin local concentrations in the tumor, by comparing HPLC and histological measurements. This method is a promising approach for imaging drug efficacy and real-time evaluation of chemotherapeutic protocols [79]. Langereis and Grüll monitored, by MRI, the controlled release of drug from a temperature-sensitive liposome with commutative imaging capabilities. The chemical exchange saturation transfer (CEST) signal was replaced by the $^{19}F$ MRI signal upon reaching the melting temperature of the lipid membrane, following the application of high-intensity focused ultrasound and was correlated with the drug release 80, 81].

Although ultrasound imaging allows real-time imaging, ultrasound contrast agents consist mostly of gas microbubbles that, even when associated with a drug moiety, are not, strictly speaking, nanomedicines. However, perfluorocarbon nanoemulsions were designed to become gaseous when insonified, as a result of the combined effects of local increased acoustic pressure and temperature. This phenomenon is called acoustic droplet vaporization (ADV). A droplet to bubble conversion, followed by cavitation, inducing the release of thrombin was observed by Fabiilli et al. [82].

Optical imaging was also considered as a visualization modality in nanotheranostics, but the strong scattering properties of soft tissues in the visible region of the light spectrum (<700 nm) limit its application. However, scattering decreases at longer wavelengths in the near-infrared (NIR) region (700–900 nm), often called "biological window" for optical imaging and many fluorophores were designed accordingly [76]. The organic NIR dye Cy5.5 was used by Kim et al. to label paclitaxel-loaded chitosan-based nanomedicines. In vivo, NIR fluorescence clearly allowed tumor delineation and signal intensity was found to be correlated with nanomedicine concentration. Optical imaging has also made it possible both to follow nanomedicine biodistribution and to monitor non-invasively tumor growth rate in response to treatment (Fig. 5) [83]. Optical NIR probes other than organic dyes, such as gold nanoparticles or quantum dots, can also be loaded into nanomedicines. Nevertheless, since penetration depth of NIR light in tissue is less than 1 cm, the observed tissues must be located close to the radiation source. At present, the clinical use of optical imaging remains limited [76].

## Conclusion

In the wake of pioneering work in the seventies, the imagination and creativity of pharmacists, chemists and engineers has led to the development of thousands of nanomedicines in the endeavor to solve issues such as drug toxicity, poor bioavailability, poor stability and deleterious side effects. Nanomedicines are made from organic and inorganic materials and their size, shape and surface chemistry may be adjusted for specific applications. Although most nanomedicines were initially intended for intravenous delivery, oral, ocular or pulmonary administration may be considered and nanomedicine properties should be tuned accordingly. The new avenues of stimuli-responsive nanomedicines and nanotheranostics seem particularly interesting and remain to be fully explored. In particular, nanotheranostics could be designed to specifically interact with malignant cells, image them, trigger a therapeutic response and monitor it in real time. Overall, nanomedicines will be upgraded from preclinical research to clinical application if the toxicity issues are better predicted and the scale-up and engineering of these complex structures prove profitable.

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**Animal and human studies** All institutional and national guidelines for the care and use of laboratory animals were followed. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for their inclusion in the study.

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