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Nanocarriers for Anticancer Drugs - New Trends in Nanomedicine

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Abstract: This review provides a brief overview of the variety of carriers employed for targeted drug delivery used in cancer therapy and summarizes advantages and disadvantages of each approach. Particularly, the attention was paid to polymeric nanocarriers, liposomes, micelles, polyethylene glycol, poly(lactic-co-glycolic acid), dendrimers, gold and magnetic nanoparticles, quantum dots, silica nanoparticles, and carbon nanotubes. Further, this paper briefly focuses on several anticancer agents (paclitaxel, docetaxel, camptothecin, doxorubicin, daunorubicin, cisplatin, curcumin, and geldanamycin) and on the influence of their combination with nanoparticulate transporters to their properties such as cytotoxicity, short life time and/or solubility.

Keywords: Nanotechnologies, nanoparticles, gene therapy, anticancer drugs, drug carriers, cancer, cytostatic, targeted therapy.

1. NANOMEDICINE

Nanomedicine is the newest member of molecular nanotechnology branches. It serves for monitoring, repairing, building, and control of biological systems on molecular level, carried out by nanocomponents and nanosystems (Fig. **1**). While molecular nanotechnology operates within the range from hundreds, thousands nanometers, the basic structural element of molecular nanotechnology is an atom with diameter less than one nm [1-4]. Dramatic advancement of these technologies can be expected, especially in diagnostics of diseases at their early stages [5-9]. Nowadays, nanomedicinal approaches can be divided into two sections: i) currently used and ii) real future perspectives. In the approaches with real future perspectives, therapeutic abilities may be seen in the nanorobots in microsurgery and in the treatment of various types of diseases, such as coronary thrombosis or malignant tumors. It may be expected that medicinal nanorobots with the size up to 1,000 nm can be injected into human body (some milliards of nanorobots correspond to one milliliter). Thus, they can support immune system, participate in processes of metabolism, perform repairing operations, eventually cluster together into higher structures and form more complicated and effective repairing and protective systems. Bio-implants in the field of skin regeneration (special polymers, silver nanoparticles) are very important nanomedicinal currently used group.

Nanodelivering of a drug belongs to other nanomedicinal group which has gained a great attention of researchers. The development of each new drug has basically two main aspects – maximal effectiveness against the existing disease and as minimal side effects (effect on non-target tissues) as possible (Fig. **2**). However, some difficulties related to drug delivery may occur, such as troublesome solubility and biological availability, short time of circulation in blood, and inconvenient biodistribution to the target organ. Nanoparticle-mediated targeted delivery of drugs might significantly reduce the dosage, optimized drug loading and release properties, increase its specificity and bioavailability, including shelf-life, and reduce the toxicity [10-12]. These nanoparticles advantages as carriers for drugs make them promising candidates to overcome cancer drug resistance [13]. As the diseases are concerned, in cancer therapy, targeted delivery in a localized way is one of the key challenges. Tumor targeting with nanoparticles can be realized through passive and active way [12, 14-16]. The particles can be modified with various types of materials including biomolecules (Fig. **3**). Using various organizations of atoms, resulting properties of particular material, such as elasticity, plasticity, strength, or conductivity are modified.

The improvement in cancer therapy is based on the enhanced permeability and retention (EPR) effect of the vasculature surrounding tumors. The active way relies on ligand-directed binding of nanoparticles to receptors expressed by tumor cells [17]. These ligands comprise antibodies, peptides, nucleic acid aptamers, carbohydrates, and small molecules [11]. The key features of anticancer nanoparticles are mainly nanoparticles size, surface properties (e.g. hydrophobicity), and targeting ligands (Fig. **3**). Generally, 200 nm is considered as upper limit for nanoparticles size, while the minimal diameter should be about 10 nm. Certainly, nanoparticles properties requirements also depend on tumor characteristics including cancer type, stage of disease, site in the body and host species (reviewed by Adiseshaiah *et al*. [18]).

Nanoparticles designed for tumor targeted therapies consist of various components, in most cases of nanocarrier and an active agent (drug) [19]. Drug-carrier nanoparticles are considered as submicroscopic colloidal systems that may act as drug vehicles, either as nanospheres (matrix system in which the drug is dispersed) or nanocapsules (reservoirs in which the drug is confined in hydrophobic or hydrophilic core surrounded by a single polymeric membrane) [20]. Nanoparticle carriers are mostly composed of iron oxides, gold, biodegradable polymers, dendrimers, lipid based carriers such as liposomes and micelles, viruses (viral nanoparticles), and even organometallic compounds [11, 21, 22]. A detailed review about nanocariers was recently published by Peer *et al* [23]. The drug encapsulation in nanocarrier provides better biocompatibility and hence potential use in clinical oncology. Several such engineered drugs are already in clinical practice, including liposomal doxorubicin and albumin conjugate paclitaxel [24]. However, the potential success of these particles in the clinic relies on consideration of above mentioned important parameters and - most importantly- minimum toxicity of the carrier itself [25]. Concerning the

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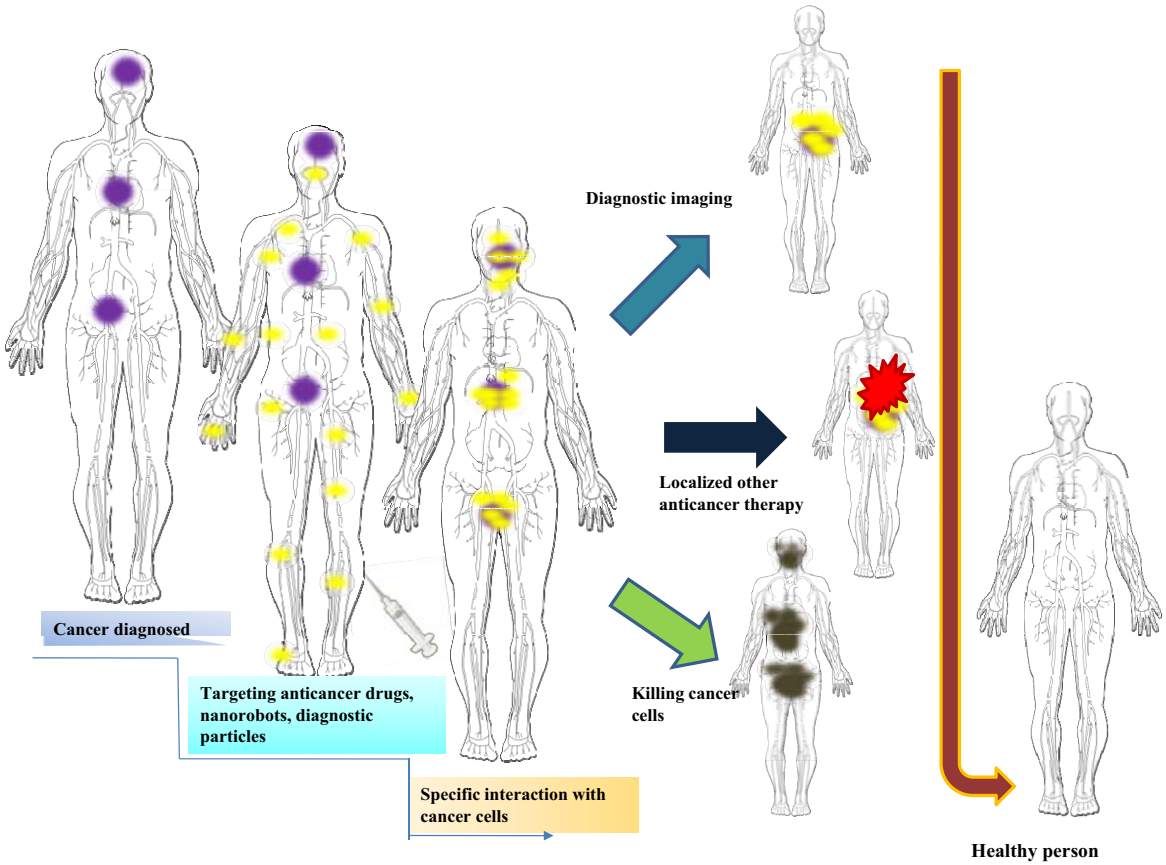

Fig. (1). Advanced nanomedicine will be able to do a much sooner diagnosis and/or to treat cancer disease. A patient who is suspected of cancer will likely undergo an application (targeting anticancer drugs, nanorobots, diagnostic particles) into the bloodstream. Then, special particles specifically interact with cancer cells. The obtained effect may be used for: a) diagnostic imaging (sensor test chips containing thousands of nanowires, able to detect proteins and other biomarkers left behind by cancer cells, could enable the detection and diagnosis of cancer at the early stages from a few drops of a patient's blood), b) localized other anticancer therapy (chemotherapy, brachyotherapy), and or c) killing all cancer cells in human body. The final stage will be curing patient.

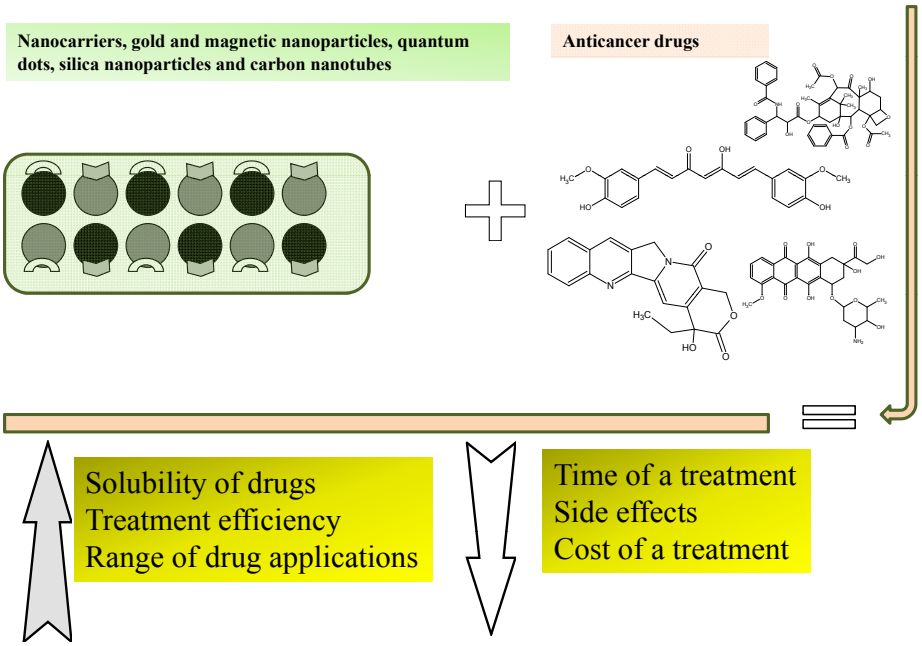

Fig. (2). Using of various types of carriers based on nanotechnologies for loading drugs can bring several advantages, including the increasing solubility of drugs, treatment efficiency and range of drug applications, and decreasing time of a treatment, side effects and cost of a treatment. All of these beneficial effects can be considered as basic building blocks for personalized medicine.

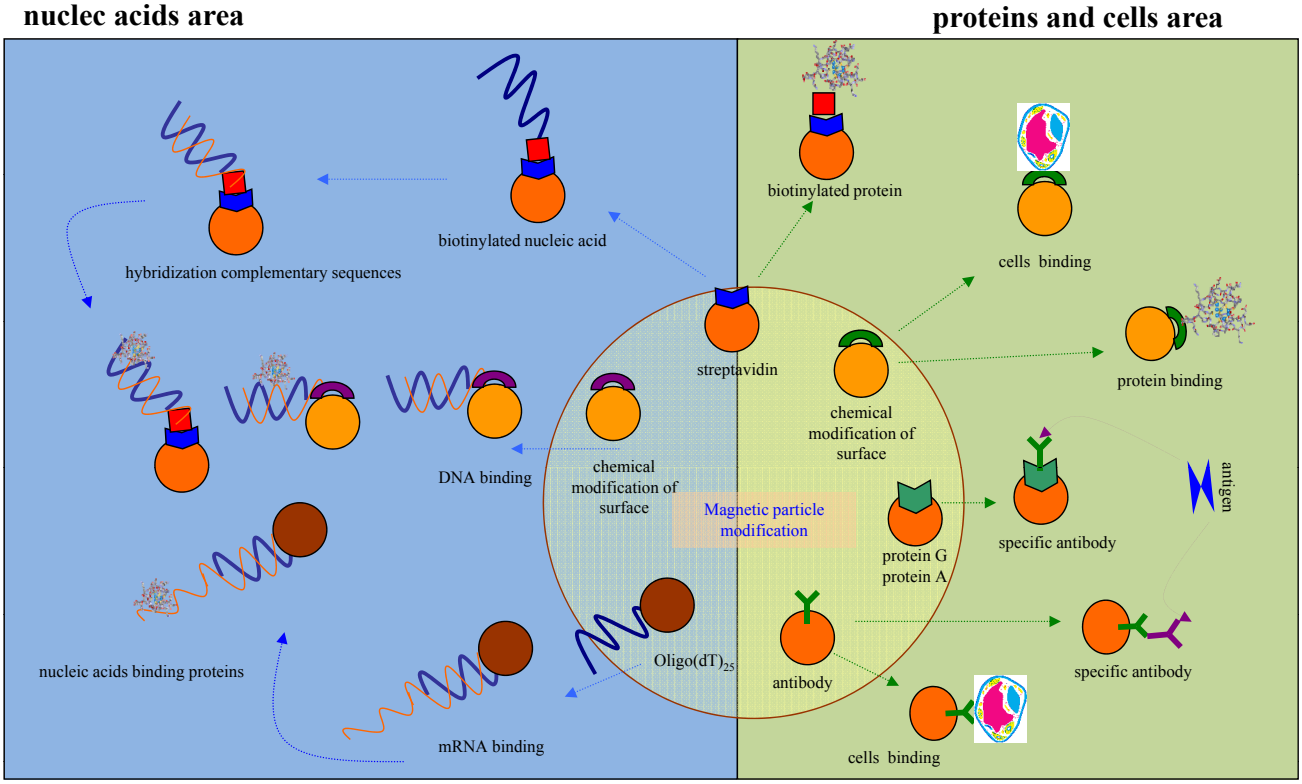

Fig. (3). Magnetic particles and nanoparticles (MNPs) as unique and versatile tools for bioassays and delivering. MNPs can be divided accordingly on MNPs modified by nucleic acids (blue box) or MNPs modified by proteins (yellow box). The basic types of modifications are given in the circle. Nucleic acids area: the beads bearing covalently attached oligo(dT)25 chains can bind nucleic acid involving (A)n stretches, including natural eukaryotic mRNAs or tDNAs tagged with (A)n adaptors. The modification enables to follow binding cell mRNA, monitoring mRNA interactions, and studying of binding peptides and proteins. MNPs with polymers anchored on their surface enable binding cell DNA (free circulating DNA) and determining DNA interactions with peptides and proteins. Streptavidin-coated beads are very important, because they are suitable for capturing any biotinylated molecules including DNA. Protein and cells area: Antibodies can be attached to the beads either *via* a direct covalent linkage, or *via* specific antibody binding proteins, such as protein A or protein G (beads functionalized with the latter proteins can be further modified with various antibodies on demand). Modified MNPs can be then used for capturing of cells including cancer ones or for binding with other specific antibodies. Other polymeric modifications of MNPs surface can be used for capturing of target proteins or whole cells. Streptavidin modified MNPs are suitable for capturing of biotinylated peptides and proteins. Adopted and modified according to [16]. (The color version of the figure is available in the electronic copy of the article).

nanoparticles´ shape, following nanostructures are frequently cited in literature: nanoshells, nanorods, nanocages, nanocubes, and nanotubes.

2. NANOCARRIERS FOR ANTICANCER DRUGS

As mentioned above, nanomedical approaches to drug delivery center on the developing nanoscale particles or molecules to improve the bioavailability of a drug at specific places in the body and over a period of time [26]. The bioavailability refers to the presence of drug molecules in the place of need in the body which provides maximal effect. This can be achieved by molecular targeting using nanoengineered devices [27, 28]. The potency of drug delivery systems is their ability to alter the pharmacokinetics and biodistribution of the drug. Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm. Efficiency is important because many diseases depend upon processes within the cell and can only be impeded by drugs delivered into the cell. Triggered response is one of the possibilities for drug molecules to be used more efficiently. The substances are placed in the body and are waiting there on encountering a particular signal. A drug with poor solubility will be replaced by a drug delivery system where both hydrophilic and hydrophobic environments exist, improving the solubility. Some drugs may cause tissue damage, but regulated drug release can eliminate the problem. If a drug is cleared too quickly from the body, this may force a patient to use higher doses, but with drug delivery systems clearance can be reduced by altering the pharmacokinetics of the drug. Potential nanodrugs will work by very specific and well-understood mechanisms. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties [29].

2.1. Polymeric Nanocarriers

Different nanoparticles have been developed using different polymers with or without surface modification to target tumor cells both passively and/or actively. Nanoparticles as drug carriers can be formed from both biodegradable and non-biodegradable polymers. Recently, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled drugs release, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in view of their ability to deliver proteins, peptides and genes through the peroral route [3, 127, 163].

New bio-applicable polymers represent a wide group of nanocarriers for application in nanomedicine and molecular biology. It

concerns mainly soluble polymer nanoparticles: liposomes, micelles, polyelectrolyte complexes and hydrogels intended for local therapies in the field of targeting biologically active molecules of epidermis. The drug is bound to the polymer system that behaves in other way than the original preparation itself. Binding of drug to the carrier leads to the suppression of its unwanted physicochemical properties (e.g. low solubility) and to the extension of circulation time in blood. Moreover, the binding enables especially targeted delivery of the drug into the tissue (e.g. tumor) and its controlled releasing in the desired location. Stolnik *et al*. showed more than three times higher circulation time of the nanoparticles compared to drugs itself [30].

When projecting the polymer carrier systems for various types of drugs, the whole series of polymers have been studied, differing in nature and structure. Some nanosystems suitable for drug delivery are created by hydrophobic association of amphiphilic molecules. For example, the molecules having a certain part strongly hydrophobic and the rest of molecule is strongly hydrophilic, like in the case of micelles and liposomes. These lipid-based nanoparticles are considered as the least toxic for *in vivo* applications and significant progress has been made in the area of drug delivery using lipid-based nanoassemblies [25].

Recently, Yallapu *et al*. summarized a novel polymeric nanocarrier based on thermo-sensitive and pH-sensitive nanogels that can be used as an ideal reservoir for loading drugs, oligonucleotides and imaging agents in cancer treatment [31]. These nanogels can further contain magnetic nanoparticles, contrast or diagnostic agents and hence they possess different biological functions for improved cancer therapeutics. The internal structure of nanogels is similar to that of hydrogels or microgels, but varies in the size and responsiveness.

Nanogels are composed of cross-linked three-dimensional polymer chain networks that are formed *via* covalent linkages or self-assembly processes. Particularly, modified polysaccharides with hydrophobic groups (e.g. cholesteryl-group modified pullulans [32]) or hydrophilic polymers of poly(N-isopropylacrylamide) [33], chitosan, dextran and poly(amino acids) using hydrophobic moieties, such as cholesteryl [34], and deoxycholic acid [35] were studied. Concerning the binding of nanogels with anticancer drugs, curcumin is one of the most frequently tested one, for example encapsulated in β-cyclodextrin or poly(β-cyclodextrin) *via* a nanoself assembly process [36].

2.1.1. Polyethylene Glycol

Polyethylene glycol (PEG) also belongs to widely used stabilizing agent [37-41]. PEG can be conjugated with many anticancer drugs and their derivatives (camptothecin, doxorubicin, paclitaxel; Fig. **4**) due to its ability to prevent drug excretion by kidney and degradation by the biological environment [42]. Generally, PEG itself does not serve as nanocarrier for anticancer drug, but it is often their important component. Recently, PEG was used to coat stimuli-responsive nanogels, which serve as nanocarriers for anticancer drug as described above. For example, Oishi and Nagasaki studied the nanogels complex containing cross linked poly(2-[N,N-diethylamino]ethyl methacrylate) core and PEG tethered chains with protected and unprotected functional groups. These nanogels with extremely high dispersion stability can be applied as magnetic resonance spectroscopic imaging probe to visualize acidosis (tumor tissue). Further, these nanogels can be employed for intracellular drug and small interfering RNA (siRNA) delivery in gene therapy and as apoptosis probe for monitoring response to cancer therapy. They can be also used as antennas for cancer photothermal therapy [43]. Lia *et al*. prepared the nanovesicle carriers from the amphiphilic block copolymer of PEG-poly(ethylene glycol)-poly(D,L-lactic acid) by a double emulsion technique. They chose gemcitabine as the model anticancer drug. Viability test demonstrated that gemcitabine-loaded nanovesicles exhibited dose-dependent and time-delayed cytotoxicity in the human pancreatic cancer cell line SW1990 and their cytotoxicity was similar to free gemcitabine [44]. Zhu *et al*. prepared folate(FA)-conjugated star-shaped copolymer nanocarrier for anticancer drug delivery by ring-opening polymerization of L-lactide using pentaerythritol as an initiator, followed by conjugation with methoxy-PEG (MPEG) and FA-PEG. The resulting amphiphilic copolymer was shaped into drug-loaded micelles with final average size of around 146 nm. It was found that the sustained release time of model drug (indomethacin) from some selected micelles could reach around 40 h [45].

2.1.2. Poly(lactic-co-glycolic Acid)

Poly(lactic-co-glycolic acid) (PLGA) represents another example of biodegradable polymers frequently used in drug delivery [46-48]. It is United States Food-and-Drug-Administration-approved hydrophobic polymer, which facilitates the biodegradation of nanoparticles and moreover provides the excellent mechanic strength of the whole nanosystem. The surface functionalization of PLGA nanoparticles has paved the way to a variety of engineered PLGA-based nanocarriers, which, depending on particular requirements, can demonstrate a wide variety of combined properties and functions such as prolonged residence time in blood circulation, enhanced oral bioavailability, site-specific drug delivery, and tailored release characteristics. Jain *et al*. reviewed the recent news in PLGA-based nanotechnology with a particular focus on cancer therapeutics [49]. Pan *et al*. used PLGA with novel biodegradable copolymer, D-α-tocopheryl PEG 1000 succinate (TPGS)-COOH allowing ligand conjugation on nanoparticles surface, in the synthesis of PLGA/TPGS-COOH nanoparticles loaded with QDs and anticancer drug docetaxel [50]. Cruz *et al*. prepared targeted nanovaccine carriers using biodegradable poly(D,L-lactide-co-glycolide) containing superparamagnetic iron oxide particles (SPIO) and fluorescently labeled antigen in a single particle [51]. The authors studied *in vivo* targeted delivery of nanovaccine carriers coated with antibodies to dendritic cells, which are the key players in the initiation of adaptive immune responses and are currently exploited in the immunotherapy against cancer and infectious diseases.

2.1.3. Dendrimers

Dendrimers belong to the polymeric materials used as the nanocarriers of anticancer drugs as well. These spherical macromolecules are repeatedly branched with the large number of peripheral groups, which open up new avenues for their various biofunctionalization or the encapsulation of hydrophobic compounds. There are two defined methods of dendrimer synthesis, divergent synthesis and convergent synthesis. However, because the actual reactions consist of many steps needed to protect the active site, it is difficult to synthesize dendrimers using either method [52, 53].

The dendrimers consist of a central core, branching units and terminal functional groups. The core together with the internal units determine the environment of the nanocavities and consequently their solubilizing properties, whereas the external groups the solubility and chemical behavior of these polymers. Liquid crystals combine the properties of both liquid and solid states. They can be made to form different geometries, with alternative polar and nonpolar layers (i.e., a lamellar phase) where aqueous drug solutions can be included [54]. Thanks to their unique physical properties (monodispersity, water solubility and encapsulation ability), these macromolecules are very promising candidates to be drug delivery vehicles [55].

Poly(amidoamine) (PAMAM) is most widely used nanoscopic dendrimer [56, 57]. Shen *et al*. studied the stabilization of noble metal (gold and silver) nanoparticles with glycidol hydroxyl-terminated PAMAM dendrimers, which acted both as stabilizers and reducing agents [58]. Another representative of dendrimers was tested by Myc *et al*., who formulated anticancer gene therapy by siRNA nanoparticles with poly(propylene imine) (PPI) and then caged them with a dithiol containing cross-linker molecules fol-

lowed by coating with PEG [59]. PAMAM dendrimer was also successfully used to carry antileukemic drug 6-mercaptopurine [60] and platinum based cytostatics [61].

2.1.4. Hydrogels

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of large amounts of water or biological fluids absorption. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites. Hydrogels exhibit a thermodynamic compatibility with water, which allows them to swell in aqueous media. They are used to regulate drug release in reservoir-based, controlled release systems or as carriers in swelling-able and swelling-controlled release devices. On the forefront of controlled drug delivery, hydrogels as enviro-intelligent and stimuli-sensitive gel systems modulating release in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences. In these systems, the release can be designed to occur within the specific areas of the body (within a certain pH of the digestive tract) or also *via* specific sites (adhesive or cell-receptor specific gels *via* tethered chains from the hydrogel surface). Hydrogels as drug delivery systems can be very promising materials if combined with the technique of molecular imprinting (MIP) [62-73].

MIP technology has an enormous potential for creating satisfactory drug dosage forms. MIP involves forming a pre-polymerization complex between the template molecule and functional monomers or functional oligomers (or polymers) with specific chemical structures designed to interact with the template either by covalent, non-covalent chemistry (self-assembly) or both. Once the pre-polymerization complex is formed, the polymerization reaction occurs in the presence of a cross-linking monomer and an appropriate solvent, which controls the overall polymer morphology and macroporous structure. When the template is removed, the product is a heteropolymer matrix with specific recognition elements for the template molecule [74].

The first example of MIP-based drug delivery systems involves rate-programmed drug delivery, where drug diffusion from the system has to follow a specific rate profile. The next example is activation-modulated drug delivery, where the release is activated by some physical, chemical or biochemical processes. And the last one is feedback-regulated drug delivery, where the rate of drug release is regulated by the concentration of a triggering agent, such as biochemical substance. Despite the already developed interesting applications of MIPs, the incorporation of the MIP approach for the development of drug delivery systems is the following step. Among the evolution lines that should contribute more to enhance the applicability of imprinting for drug delivery, the application of predictive tools for a rational design of imprinted systems and the development of MIP in water may be highlighted [75-78].

Zhao *et al*. tested injectable hydrogel with hydrophobic microdomains for incorporating two anticancer drugs, doxorubicin hydrochloride (DOX) and paclitaxel (PTX). Injectable gels were synthesized from glycol chitosan and benzaldehyde terminated poly(ethylene glycol)-block-poly(propylene glycol)-block-poly (ethylene glycol) *via* Schiff's reaction triggered by environmental pH. By intratumoral administration, the hydrogel-drug formulations resulted in the efficient growth inhibition of subcutaneous tumor (B16F10) on C57LB/6 mouse model. The advantage of the current system for DOX + PTX combination therapy was demonstrated by a prolongation of survival time in comparison with the single drug therapy [79].

2.2. Lipid Nanocarriers

Lipid nanocarriers cover a broad scale of various systems, particularly lipid nanocapsules, micelles and liposomes, which can be used for the encapsulation of drugs that selectively target malignant cells. Lipid nanocapsules are produced through a phase inversion process that follows the formation of an oil/water microemulsion containing an oily fatty phase, a non-ionic hydrophilic surfactant and a lipophilic surfactant. They can be adjusted from 20 to 100 nm with a narrow distribution. They can enter into the intracellular compartment of cancer cells, escape from lysosomes and improve the activity of a number of anticancer hydrophobic compounds. For example, Weyland *et al*. developed safe nanocarriers for administration of SV30, which is a new analogue of the pro-apoptotic molecule HA14-1. They observed that SV30 alone or in combination with paclitaxel, etoposide or beam radiation could trigger cell death in a similar fashion to HA14-1 [80].

2.2.1. Liposomes

Liposomes belong to the simplest and longest used nanocarriers [81, 82]. Liposomes are hollow balls circumscribed by amphipathic phospholipid bilayer that is very similar to the cytoplasmatic membrane (Fig. **4**). Depending on the size and the number of phospholipid bilayers, liposomes can be classified into small unilamellar vesicles (single lipid layer from 25 to 50 nm in diameter), large unilamellar vesicles and multilamellar vesicles (several lipid layers separated one from another by a layer of aqueous solution). The total size of liposome structure is about 100–150 nm.

Liposomes are mainly used to solubilize drugs providing their better biodistribution as compared to free drug [83, 84]. Depending on its nature, the drug is dissolved either in the lipid bilayer (for more hydrophobic drugs, less used) or in water core of liposome (for more hydrophilic drugs, more often used) [29]. They are currently investigated for the delivery of vaccine, toxoids (bacterial toxin) as well as gene [85-88], anticancer [89-93], and anti-HIV drugs. Due to the ability of liposomes to withstand enzymatic cleavage, the liposome-drug complex can be applied directly into circulation. However, the usage of liposomes as drug carrier is limited by the rapid clearance from the circulation by the reticuloendothelial system [42]. Their blood circulation time can be increased through surface modification (e.g. by attaching PEG, dextran, or poly-N-vinylpyrrolidones to the lipid bilayer). Furthermore, conjugation with targeting ligands, like monoclonal antibodies or aptamers, can enhance their tissue specificity [22].

Some important characteristics of liposomal cocktails involving the combination of two cytotoxic drugs were recently reviewed by Chiu [94]. Chen *et al*. developed As_2O_3 nanoparticles with anticancer ability encapsulated in 100 nm scale, folate-targeted liposomes to lower systematic toxicity and provide a platform for targeting this agent [95]. Ashley *et al*. reported on the porous nanoparticle-supported lipid bilayers - so called protocells - that synergistically combine properties of liposomes and nanoporous particles. Protocells can be loaded with the combinations of therapeutic (drugs, siRNA and toxins) and diagnostic (quantum dots) agents. The high surface area of nanoporous core combined with the enhanced targeting efficacy of the fluid supported lipid bilayer enable a single protocell loaded with a drug to kill a drug-resistant human hepatocellular carcinoma cell, thus representing a 10^6-fold improvement over comparable liposomes [96].

Bedi *et al*. studied a novel approach for the intracellular delivery of siRNAs, which is potential anticancer therapeutic, into the breast cancer cells through their encapsulation into the liposomes targeted to the tumor cells with preselected intact phage proteins [97]. The targeted siRNA liposomes were obtained by a fusion of two parental liposomes containing spontaneously inserted siRNA and fusion phage proteins. Recently, Abu Lila *et al*. designed PEG-coated cationic liposome to achieve the dual targeting delivery of l-OHP to both tumor endothelial cells and tumor cells in a solid tumor [98]. The targeted liposomal l-OHP formulation showed an efficient antitumor activity in a murine tumor model after three sequential liposomal l-OHP injections. Cumulative cytotoxic effects of l-OHP delivered by PEG-coated cationic liposomes led to the

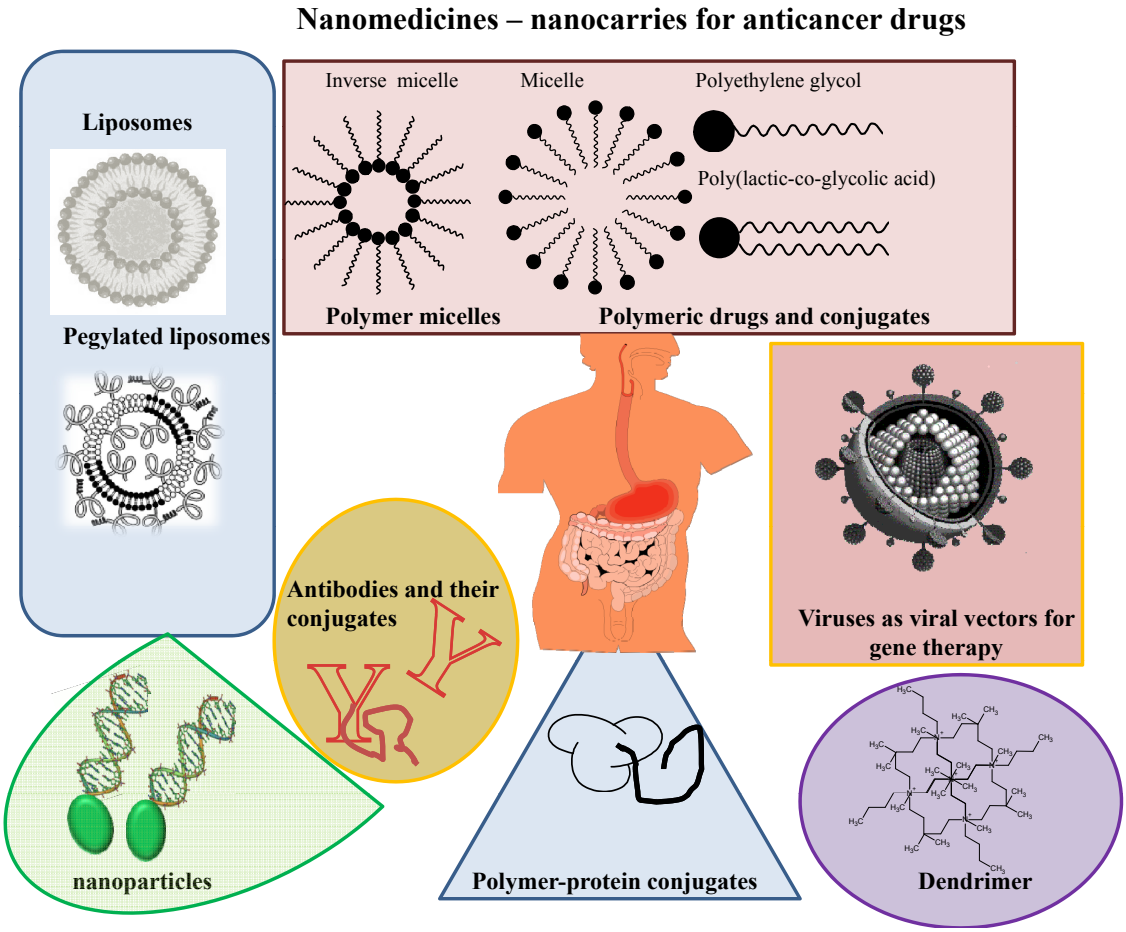

Fig. (4). Nanomedicines - nanocarries for anticancer drugs. Liposomes and pegylated liposomes (blue box) have a surface structure consisting of lipid bilayer and inside the cavity can carry a number of hydrophobic anticancer drugs. Polymeric micelles and polymeric drugs and conjugates (purple box) allow for easy anchoring and drug transport to the cell compartments, viruses and viral vectors for gene therapy (pink box). Dendrimers (dark purple box) offer a variety of ways to capture targeted anticancer drugs. Polymer-protein conjugates (light blue triangle) with synthetic molecules are used to increase the efficiency of therapeutic molecules. Antibodies and their conjugates (orange circle) increase the selectivity of target drugs only to cancer cells. Nanoparticles (green oval) - through their modification of the surface - offer new tools for drugs delivering. (The color version of the figure is available in the electronic copy of the article).

deep diffusion of a subsequent dose of liposomal l-OHP in solid tumor, presumably as a result of the enlarged intra-tumoral interstitial space.

2.2.2. Micelles

Micelles are particles with the size of several tens of nanometers and with hydrophobic tail and hydrophilic head (Fig. **4**). They are usually used as carriers of hydrophobic drugs and can be applied directly into the circulation like liposomes. The advantage of polymer micelles is their high relative molecular weight that enables preferred storage in the tissue of solid cancers using EPR [99, 100]. The vessels in solid cancers are significantly more permeable and "leaky" for the big molecules than the vessels in healthy tissue due to the rapid growth of cancer. Moreover, in the cancer affected tissues, the lymph is unable to drain properly. This results in strong accumulation of big macromolecules and above-molecular formations like micelles in the tumor tissue much more easily than in any other tissue. Their concentration is often one order higher than in the surrounding area. Therefore, the cytostatics cumulate in the close neighborhood of the fast growing cancer cells together with micelles, while the remaining non-accumulated micelles stay in the blood vessels, being removed by kidney filtration after unimer (non-organized polymer chains in micelles) disaggregation.

The drug can be bound in the micelle either hydrophobically (i.e. dissolved in the micelle core), or can be directly chemically bound on the polymer carrier by enzymatic biodegradable bond. The first method is more universal and simple but it is more complicated to control the rate of drug release from the polymer micelle. On the other hand, the chemical bond enables taking control of drug release rate and its activation just in the tumor tissue so that there is no drug release during its circulation in the blood. The creation of hydrazon bond is one of the possible mechanisms. This bond is hydrolitically unstable under slightly acidic conditions (tumor tissue is much more acidic than blood plasma due to hypoxia), while it is more stable under the neutral conditions in the blood.

Chandran *et al*. designed the complex micelle structure: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)2000]/D-alpha-tocopheryl polyethylene glycol 1000 (PEG-DSPE/TPGS) as nanocarriers for 17-Allyamino-17-demethoxy-geldanamycin, an anticancer drug [101]. They tested cytotoxicity of this drugs mixed with micelles against human ovarian cancer SKOV-3 cells.

Xu *et al*. reported on the preparation and physical and biological characterization of the human serum albumin-based micelles (with diameter of about 30 nm) for the delivery of amphipathic drugs. The micelles were conjugated with cyclic RGD (arginine–

glycine–aspartic acid) peptides and selectively delivered to the cells expressing the alpha(v)beta(3) integrin. PEGs were used to form a hydrophilic outer layer, with the inner core formed by albumin conjugated with doxorubicin *via* disulfide bonds. Additional doxorubicin was physically adsorbed into this core to attain a high drug loading capacity, where each albumin was associated with about 50 doxorubicin molecules [102]. Poon *et al*. synthesized a novel linear-dendritic block copolymer for targeted delivery of paclitaxel. They found these drug loaded nanocarriers to have prolonged accumulation time in the tumor up to 5 days compared with non-targeted vehicles [103].

2.3. Hydroxyapatite

Venkatesan *et al*. investigated chitosan modified hydroxyapatite nanocarriers loaded with celecoxib, which is a potential anticancer drug against most carcinomas, especially in patients with familial adenomatous polyposis and precancerous disease of the colon. Nanoparticles exhibited small, narrow hydrodynamic size distributions, hemocompatibility, high entrapment efficiencies and sustained release profiles [104]. Similarly, Wang *et al*. fabricated flower-like nanostructured hydroxyapatite hollow spheres (NHHS) as carriers for the cellular delivery of anticancer drug mitoxantrone [105].

2.4. Gold Nanoparticles

Recently, gold nanoparticles (AuNPs) have been studied in biological and photothermal therapeutic contexts [106, 107]. This interest is motivated by the capability of AuNPs to bind a wide range of organic molecules, their low level of toxicity, and strong and tunable optical absorption [108]. AuNPs can be used as drug [109] and vaccine carriers into target cells or specific tissues. Generally, this has been achieved by modifying the surface of the AuNPs so that they can bind to the specific targeting drugs or other biomolecules. AuNPs can be directly conjugated with antibiotics or other drug molecules *via* ionic or covalent bonding [110] or by physical absorption [111]. The release of a drug from AuNPs could proceed *via* internal stimuli (operated within a biologically controlled manner, such as pH) or *via* external stimuli (operated with the support of stimuli-generating processes, such as the application of light) [112]. AuNPs size is generally about 50 nm, which is smaller than other nanomaterials like core/shell nanostructures [38, 39]. For example, gum arabic glycoprotein functionalized AuNPs possess optimum sizes (core diameter of 12–18 nm and hydrodynamic diameter of 85 nm) to target individual tumor cells and penetrate through tumor vasculature and pores [113].

Gold hollow nanostructures represent a new class of metal nanomaterials suitable for anticancer drug encapsulation. These materials have ideal optical properties with strong absorption in near infrared (NIR) region (700–900 nm) which makes them attractive candidates for photothermal therapy of cancer and surface enhanced Raman spectroscopy (SERS) for *in vivo* cancer biomarker detection [114]. Photothermal therapy is a minimally invasive treatment method, where photon energy is converted to thermal energy sufficient to induce cellular hyperthermia. Selectivity is achieved by directional control or invasive positioning of the incident radiation (pulsed or continuous wave laser), and is typically accompanied by preferential administration of photoactive molecules or nano-scale particles. Photoexcitation by the laser results in non-radioactive relaxation and local heat transfer to the surrounding tumor environment [115].

Wang *et al*. prepared size-controlled supramolecular AuNPs as a photothermal agent for the targeted photothermal treatment of certain types of cancer cells [106]. They used RGD peptide ligand to target $\alpha_v\beta_3$-positive/negative cells as the corresponding biological system to test the specificity and selectivity of RGD-AuNPs. They observed selective damage of the $\alpha_v\beta_3$-positive cells and no damage of neighboring $\alpha_v\beta_3$-negative cells. The photothermal ablation of solid tumors was also investigated by Goodrich *et al*., who tested NIR absorbing gold nanorods coated with PEG [37]. The cytotoxicity of residual cetyltrimethylammonium bromide (CTAB), which is used in the nanorods manufacture, is also discussed regarding the presence of PEG coating [116]. They found that the diafiltration is successful method for CTAB excess removing and thus enables safety use of chosen gold nanoparticles. They also discussed possibility of AuNPs modification with antibodies against tumor cells [10].

Wang *et al*. developed a drug delivery system that tethers doxorubicin onto the surface of AuNPs with PEG spacer *via* an acid-labile linkage [117]. They demonstrated that multidrug resistance in cancer cells can be significantly overcome by a combination of highly efficient cellular entry and a responsive intracellular release of doxorubicin from AuNPs in acidic organelles.

2.5. Magnetic Nanoparticles

The usage of magnetic nanoparticles (MNPs) made of pure iron oxide in targeted and controlled drug delivery is limited mainly due to their insufficient biocompatibility [12, 118, 119]. Therefore their modification with various materials, e.g. polymers, is unavoidable. MNPs can be used for targeting in drug and gene delivery in the case of various diseases, including cancer (Fig. **5**). Magnetic field (represented by a magnet) allows passing MNPs through the cell membrane and reaching the nucleus [120]. Chemical drug (anticancer drug, e.g. doxorubicin), biological drug (therapeutic specific proteins or peptides), nucleic acids (siRNA, antisenseRNA, DNA) and monoclonal antibodies are anchored on MNPs to increase the selectivity of target drugs to tumor cells.

Apatite coated bioactive and superparamagnetic particles were used and evaluated as potential materials for bone cancer treatment [121]. Zhang *et al*. synthesized tetraheptylammonium capped magnetic nano Fe_3O_4 and studied *in vitro* anticancer drug accumulation inside leukemia K562 cell lines. The observations indicated that the tetraheptylammonium-capped nano Fe_3O_4 could efficiently enhance the relevant drug permeation into cancer cells through internalization endocytosis processes and result in the significantly enhanced doxorubicin uptake in relevant leukemia K562 cells [122]. Cheng *et al*. recently developed very interesting multifunctional nanoparticles with combination of chemotherapeutic and NIR photothermal cancer therapy [46]. The complex nanosystem consists of stabilizer-free Taxol-loaded PLGA nanoparticles conjugated with amine-terminated Fe_3O_4 MNPs and PEG-grafted CdSe QDs. This nanoarchitecture was finally functionalized with poly(styrensulfonate) coated gold nanorods, which can absorb NIR light, convert it to heat and destroy PLGA nanoparticles resulting in the release of encapsulated Taxol. The system was applied on HeLa cells with great efficiency.

Another example of multilayered nanoparticles combining magnetic core and two encompassing polymeric shells (PLGA and temperature sensitive poly(N-isopropyl-acrylamide) (PNIPAAm)) was published by Koppolu *et al*. [47]. Such nanocomposite can contain both hydrophilic and hydrophobic drugs, the first loaded into PNIPAAm MNPs, while the second (curcumin) embedded in outer PLGA layer. Dilnawaz *et al*. conjugated in their study aqueous based protein HER2 (Human Epidermal growth factor Receptor 2) glycerol monooleate coated MNPs. The obtained results showed enhanced uptake in the human breast carcinoma cell line (MCF-7), which provides another potential use for highly sensitive and selective drug target for cancer HER2 positive breast cancer [123]. Multifunctional and water-soluble SPIO nanocarriers were developed by Yang and colleagues for targeted drug delivery and positron emission tomography/MRI dual-modality imaging of tumors with integrin $\alpha_v\beta_3$ cell expression. An anticancer drug was conjugated onto the PEGylated SPIO nanocarriers *via* pH-sensitive bonds [124].

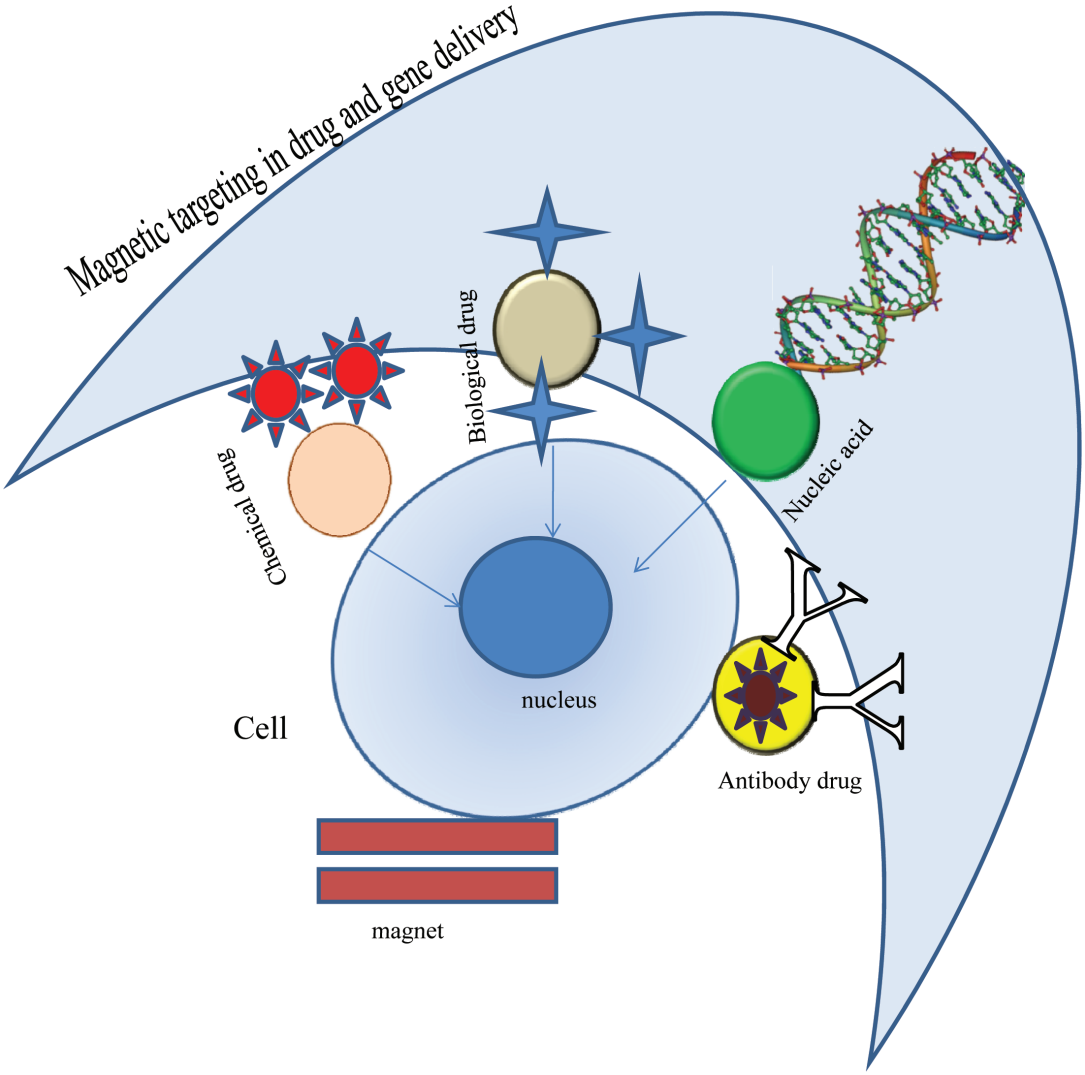

Fig. (5). MNPs (color circles) carrying nucleic acids or anticancer drugs can be magnetically guided into the cells (blue circle) using an external strong magnet. Intense magnetic field enables the penetration of nanoparticles through the cell membrane to the nucleus. The proposed procedure can be used for the treatment using both chemical and biological molecules. MNPs (brown circle) bear anticancer chemical drugs (e.g. doxorubicin); biological drugs are represented by peptides and proteins with anticancer effect (beige circle); nucleic acids (green circle) such as siRNA, antisense RNA, DNA; antibody drug (yellow circle) bear antibody against cells or nucleus specific antigens (Her 2) and, thus, they target the drug directly to the cancer tissue only, which can turn off certain genes that cause cancer diseases. Adopted according to [120]. (The color version of the figure is available in the electronic copy of the article).

2.6. Quantum Dots

The preparation of non-cytotoxic quantum dots (QDs) for molecular imaging and targeting therapy has been intensively investigated [125]. QDs were found as an alternative to the organic dyes and fluorescent proteins and thus they can be used for various biosensing purposes [12, 126]. The photo-physical properties which make QDs interesting as compared to classic organic dyes are: broad absorption spectra, very narrow emission spectra, long fluorescence lifetime, and high stability against photobleaching [127-129]. QDs have also high quantum yield, high molar extinction coefficients [130] and large effective Stokes shift [131]. QDs always emit the same wavelength of light no matter what excitation wavelength is used [132]. Therefore, multiple QDs with different emission spectra can be simultaneously visualized using a single excitation light source. The dimension of the core determines the bandgap and hence the color of emission. An increase in particle size produces a redshift in the emission spectrum [133]. In principle, the emission of QDs can be coarse-tuned by the choice of the material and later fine-tuned by playing with the size of the core [14].

The unique integration of drug targeting and visualization has high potential to address the current challenges in the cancer therapy [134, 135]. The basic principles for *in vivo* targeting and imaging of cancers using QDs are the biodistribution of QD bioconjugates, penetration depths of excitation light and photoluminescence, tissue autofluorescence, toxicity, and pharmacokinetics. Bioconjugated QDs were applied *in vivo* either systemically for deep cancers or subcutaneously for marginal cancers [136]. Yuan *et al*. prepared monodispersed ZnO QDs with strong blue emission by a chemical hydrolysis method. They described a new approach of combining QDs technology with biodegradable chitosan (N-acetylglucosamine) for tumor-targeted drug delivery. Chitosan enhanced the stability of the QDs because of the hydrophilicity and cationic charge of chitosan [137]. The encapsulation of QDs by polymers, phospholipids or inorganic shell prevents the dissociation and enables anchoring of biomolecules. Silica-shelled QDs represent probably the most attractive alternative [138]. Nurunnabi *et al.*

modified in their study the surface of NIR CdTe/CdSe QDs by the solid dispersion method using PEG-10,12-pentacosadiynoic acid (PEG-PCDA) and PCDA-Herceptin conjugates to demonstrate the water-solubility and target-specific properties. Upon UV irradiation, QD cores located within nanoprobes were further stabilized by intramicellar cross-linking between the neighboring PCDA-Herceptin moieties. These cross-linked nanoprobes showed higher stability and lower toxicity. The results of animal studies showed that NIR QDs loaded micelles have high anti-tumor activity and selective toxicity, resulting in 77.3% reduction of tumor volume [139].

2.7. Silica Nanoparticles

Silica-based nanoparticles also belong to the group of suitable nanocarriers for cancer treatment. They allow the systemic or topical administration of a photosensitive drug, so called photosensitizer (PS), into the cancer cells. The researchers coated PS filled mesoporous silica nanoparticles with lipid layer to achieve the cell membrane structure and biocompatible surfaces [140]. Zhu *et al*. loaded the Fe_3O_4/SiO_2 hollow mesoporous spheres with doxorubicin. The authors discussed the influence of particle size, mesoporous shell thickness and concentration of Fe_3O_4/SiO_2 hollow mesoporous spheres on cell uptake and on *in vitro* cytotoxicity to HeLa cells [141].

Although the potent antitumor activity of nitric oxide (NO) supports its usage as an antineoplastic agent, effective and selective delivery and the action on tumor and not on healthy cells remains a limiting factor. Silica nanoparticle based delivery of NO has been considered as an approach to overcome these limitations. The NO-releasing nanoparticles exhibited the enhanced growth inhibition of ovarian tumor cells when compared to both control nanoparticles and previously reported small molecule NO donor [142]. Further, the endocytosis and time-dependent enhanced cytotoxicity of anticancer platinum drugs combined with (or loaded into) mesoporous silica materials were reported [143].

Deng *et al*. investigated the drug nanocarriers consisting of mono-dispersed and pH sensitive chitosan-silica hollow nanospheres (CS-SiO_2 HNPs) fabricated by one step method and suitable for breast cancer therapy. The resulting SiO_2 HNPs with a pH-sensitive polyelectrolyte layer were conjugated to the antibody molecule (to ErbB 2) to produce the desired nanocarriers for targeted TNF-α drug delivery to tumor cells [144].

Yuan *et al*. prepared poly(acrylic acid) grafted mesoporous silica nanoparticles (PAA-MSNs) by a facile graft-onto strategy, i.e., the amidation between PAA homopolymer and amino group functionalized MSNs. The resulted PAA-MSNs were uniform spherical nanoparticles with a mean diameter of approximately 150 nm. Due to the covalent graft of hydrophilic and pH-responsive PAA, the PAA-MSNs could be well dispersed in the aqueous solution, which is favorable for utilization as anticancer drug carriers (doxorubicin hydrochloride) to construct a pH-responsive controlled drug delivery system [145].

Wang *et al*. reported on the fabrication of monodisperse hollow mesoporous silica (HMS) nanocages with uniform size possessing a hollow cubic core and mesoporous shell with penetrating pore channels based on a template-coating-etching process. The authors evaluated the therapeutic efficacy of doxorubicin loaded HMS nanocages *in vitro* and *in vivo* for liver cancer therapy. The results showed that the doxorubicin-loaded HMS nanocages show good cell uptake and can induce efficient cell death *in vitro* [146].

2.8. Carbon Nanotubes

Both single walled and multi walled carbon nanotubes (SWCNTs and MWCNTs) as well as a wide scale of fullerenes can be applied as carriers in specific drug delivery for cancer therapy thanks to their unique electronic, thermal, and structural characteristics [147]. In addition, their ability to strongly absorb NIR radiation and efficiently convert absorbed energy to the heat can be used for localized hyperthermia applications [148]. The researchers showed that these nanostructures can be taken up only by cancerous cell *via* their functionalization with tumor-specific ligands, such as radiation ion chelates, fluorescent probes folic acid, and monoclonal antibodies [149, 150]. Analogous to other nanostructures, the functionalization of CNTs is a key parameter to significantly reduce their toxicity and maximize the bioavailability of the anticancer drugs (proteins, nucleic acids, etc.) by improving the solubility and increasing the circulation time [151-154]. For example, Wu *et al*. combine MWCNTs functionalized with carboxylic groups with covalently attached antitumor agent 10-hydroxycamptothecin using hydrophilic diaminotriethylene glycol as the spacer between nanotubes and drug moieties [155]. Sahoo *et al*. studied carbon nanomaterials, namely MWCNTs and graphene oxide functionalized with highly hydrophilic and biocompatible PVA for loading and delivery of an anticancer drug, camptothecin to kill human breast and skin cancer cells [156].

3. SELECTED ANTICANCER DRUGS IN NANOTECHNOLOGY DELIVERY

The effectiveness of anticancer agents may be hindered by low solubility in water, poor permeability, and high efflux from cells. Drug delivery systems are designed to improve the safety and/or efficacy of the therapeutic agent, while simultaneously enhancing the patient compliance. In these days, delivering of many drugs including the most common as paclitaxel, docetaxel, camptothecin, doxorubicin, cisplatin, and curcumin is being tested. Chemical structures of paclitaxel, camptothecin, doxorubicin, cisplatin, and curcumin are shown in (Fig. **6**).

3.1. Paclitaxel

Wani and colleagues found the molecule standing behind anticancer activity of bark extracts from the Pacific Yew Tree (Taxus brevifolia) and called it “taxol” [157]. The commercial name for this drug is paclitaxel. Nowadays, it is used for the treatment of ovarian, breast, lung, head and neck, and unknown primary cancers [158]. However, a poor aqueous solubility of this drug has been for more than two decades one of the main obstacle to its wider use. Various delivery strategies have been suggested including the nanotechnologies in the form of polymer based controlled release systems. ReGel is an example of such system comprising of PLGA and PEG with the basic structure of PLGA–PEG–PLGA [159]. The system incorporating paclitaxel into ReGel called OncoGel was designed for local delivery of paclitaxel to the solid tumors to provide the targeted cytotoxicity [160]. This delivery system has been successfully utilized for treatment of several types of cancer [161-164]. Paclitaxel can be released from the ReGel for six weeks into the tumor and its surroundings. Other delivery systems decreasing adverse effects of standard paclitaxel include pastes, liposomes, conjugates with antibodies, peptides, and fatty acids, nanospheres and microspheres, cyclodextrin complexes, emulsions, mucoadhesive gel, prodrugs and nanoparticulate systems [165].

3.2. Docetaxel

Docetaxel (DTX), marketed as Taxotere®, represents another drug from the group of taxanes, extensively used chemotherapeutic agents for the treatment of solid tumors. Its efficacy has been proven against the different cancers, namely prostate and breast cancer. For example, Ostacolo *et al*. studied the efficacy of DTX loaded micelles based on poly(ethylene oxide)-poly(epsilon-caprolactone) block copolymers to growth inhibition of human breast MCF-7 and MDA-MB468 and prostate PC3 and DU145 adenocarcinoma cell lines [166].

Zhang and colleagues prepared DTX loaded micelles with or without somatostatin analogue, octreotide, to bind to somatostatin receptors (SSTRs) overexpressed on tumor cells for enhanced intra-

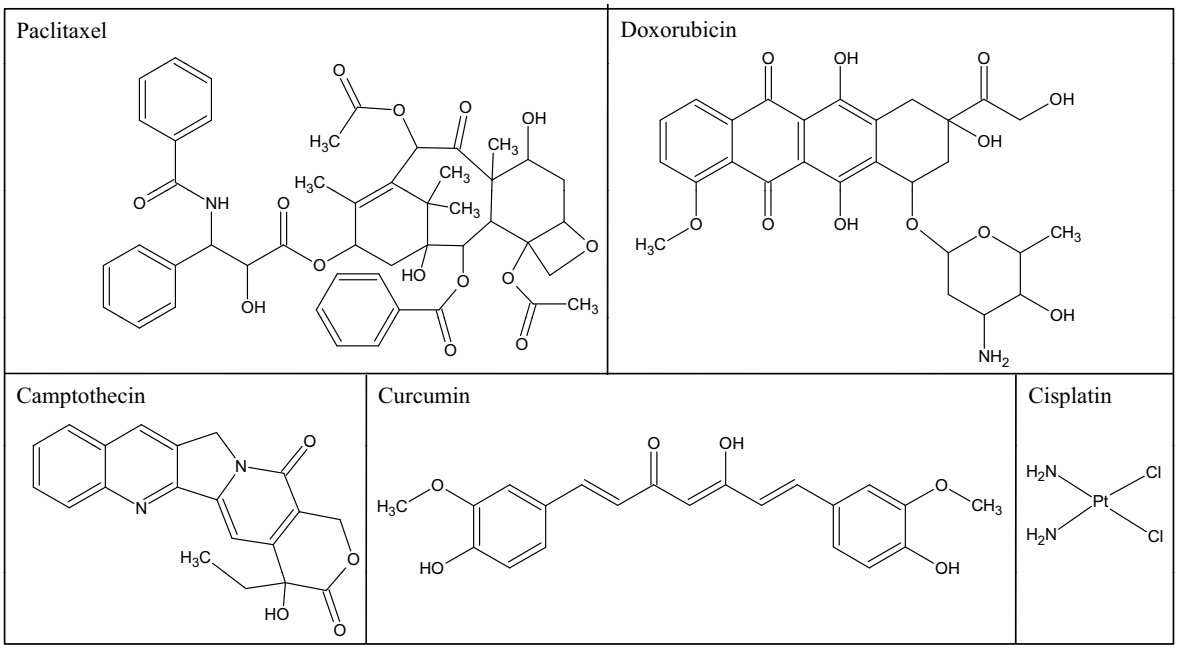

Fig. (6). Chemical structures of several most used anticancer drugs (paclitaxel, camptothecin, doxorubicin, cisplatin, and curcumin), which are tested for nanomedicinal applications. The drugs are mostly encapsulated into the liposomes or micelles, or conjugated with PEG.

cellular drug delivery and improved therapeutic efficacy for malignant tumors. All micelles were less than 80 nm in diameter, with spherical shape and high encapsulation efficiency. DTX molecules were well dispersed in the micelles without chemical interactions with the polymers. SSTRs targeting micelles may serve as promising nanocarriers in tumor treatment for hydrophobic anticancer drugs, such as DTX [167].

3.3. Camptothecin

Camptothecin (CPT) is a natural plant alkaloid extracted from Camptotheca accuminata inhibiting the activity of DNA topoisomerase I. However, it is highly toxic to normal cells, structurally instable and water insoluble and therefore effective delivery to cancer cells is challenging. Physiological conditions, such as pH equal to or above 7, causes the hydrolysis of CPT leading to the opening of the lactone ring forming the inactive carboxylate. This is even more supported by binding human serum albumin to the carboxylate form increasing the hydrolysis yield [168]. CPT based drugs, specifically irinotecan (Camptosar) and topotecan (Hycamptin) have been approved by the Food and Drug Administration [169]. CPT has been widely used in nanoparticle mediated drug delivery studies including PEG based nanoparticles [170, 171], paramagnetic Fe_3O_4 nanoparticles [172] or lipid nanoparticles [173]. Recently, synthesis of CPT loaded gold nanomaterials has been presented by Xing *et al*. [168]. The authors synthesized branched nanochains consisting of spherical nanoparticles with average diameter of 10 nm. Release of CPT and the aggregation of gold nanoparticles can be controlled by tuning the solution pH.

To circumvent insolubility, instability and toxicity of CPT, Koo *et al*. used biocompatible, biodegradable and targeted sterically stabilized micelles (SSM) as nanocarriers for CPT. They also surface-modified CPT-SSM with vasoactive intestinal peptide (VIP) for active targeting and found that CPT is efficacious against collagen-induced arthritis in mice [174].

3.4. Doxorubicin

Anthracyclines including doxorubicin (DOX) belong to antibiotics produced by *Streptomyces peucetius subsp. cesius* inhibiting the synthesis of nucleic acids. They are commonly used in the treatment of a number of diverse malignant tumors - acute leukemia, non-Hodgkin's and Hodgkin's lymphoma and several solid tumors including neuroblastoma [57, 175-178]. On the other hand, the side effect of cumulative dose dependent cardiotoxicity, myelosuppression [179] as well as large distribution volume and low life time under physiological conditions [180] represent the limitations of its clinical use. These toxic effects have been successfully reduced by employing the various nanoparticle types such as micelles, polymer based nanoparticles [181] as well as liposomes [182] and magnetic particles [183] as drug carriers.

In the study of Rai *et al*. estrogen receptor targeted liposomes encapsulating DOX was designed to enhance the delivery efficiency of doxorubicin to its destination site. The liposomal formulations showed the change in the biodistribution profile. Targeted formulation accumulated more in the breast and uterus [184].

Next, Kang *et al*. examined injectable *in situ* forming gels containing DOX as a localized drug-delivery system. These gels existed in an emulsion-sol state at room temperature and rapidly gelled *in vitro* and *in vivo* at body temperature. DOX loaded gels exhibited remarkable *in vitro* anti-proliferative activities against B16F10 cancer cells. *In vivo* experiments employing B16F10 cancer cell xenograft-bearing mice showed that a single intratumoral injection of DOX loaded gel inhibited the growth of tumors as effectively as repeated injections of free DOX, and more effectively than a single dose of free DOX, or saline or gel alone [185].

3.5. Daunorubicin

Daunorubicin is a chemotherapeutic from the anthracycline family used in the treatment of specific types of leukemia (acute myeloid leukemia and acute lymphocytic leukemia). Like DOX, it was initially isolated from Streptomyces peucetius. Wang *et al*. investigated antitumor effect of daunorubicin loaded magnetic nanoparticles (DNR-MNPs) on leukemia cells *in vitro*. MNPs were spherical and their size was from 10 to 20 nm. The average hydrodynamic diameter of DNR-MNPs in water was 94 nm. The *in vitro* release data showed that DNR-MNPs had excellent sustained release property. Proliferation of K562 cells was inhibited in a dose-dependent manner by DNR in solution (DNR-Sol) or by DNR-MNPs [186]. Li and colleagues explored the bio-application of new

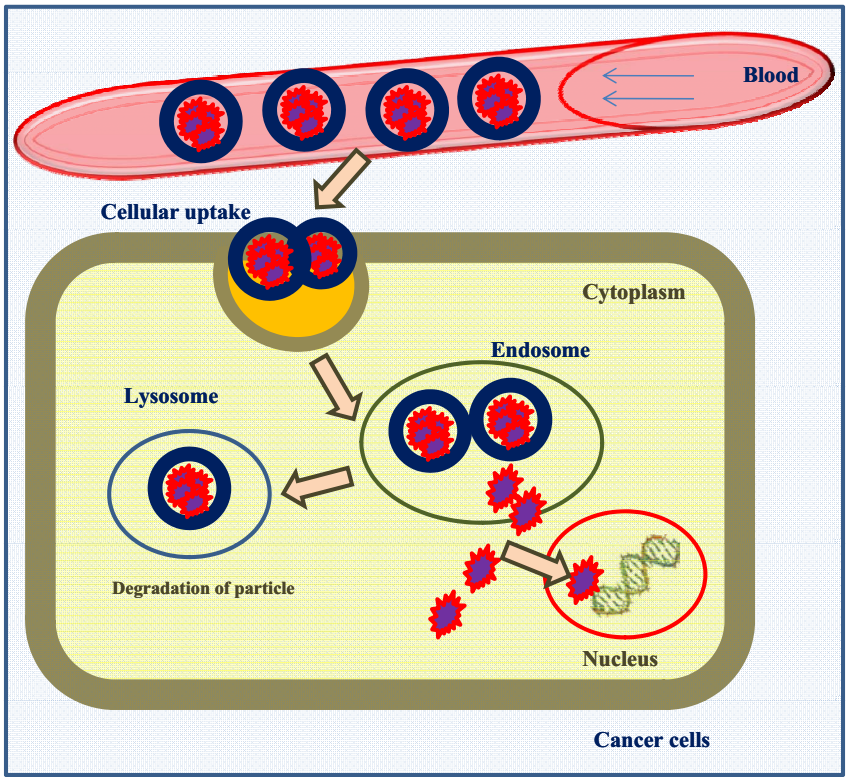

Fig. (7). Liposomes, pegylated liposomes, and polymer micelles have been widely utilized for various anticancer drugs delivery because of their high biocompatibility, resulting from their phospolipide structure. They are required to circulate in the blood and release from the blood vessel around the targeted tissues following by cellular uptake into the targeted cells for practical therapy. Moreover, intracellular delivery of the encapsulated drugs is required to exert pharmaceutical effects. The pH-sensitive liposomes composed of zwitterionic amino-acid based lipids responsible to the pH around the tumor to enhance the cellular uptake, or to the endosomal pH to control the intracellular drug delivery are developed. In lysosomes, it is likely that there will be a degradation of the applied drugs taking place. In other cellular structures, such as endosomes, drugs are released into the cytoplasm and subsequently transported into the cell nucleus, where it stops the replication and transcription, which is one of the desirable effects of treatment. Adopted and modified according to Takeoka [218-220].

nanocomposites consisting of poly(lactic acid) (PLA) nanofibers and Au nanoparticles as the potential nanocarrier for an efficient daunorubicin delivery into drug-sensitive K562 and drug-resistant leukemia K562/ AO2 cells. The authors observed that PLA/Au nanocomposites could readily induce daunorubicin to accumulate and uptake in the target leukemia cells and increase the drug's cytotoxicity [187].

3.6. Cisplatin

The biological activity of the first platinum based cytostatic drug – cisplatin (cis-diamminedichloroplatinum(II)), which is still one of the most frequently used cytotoxic agent [188-190], was discovered in 1965 by Rosenberg during his studies of an electric current effects on bacterial growth [191]. Metal organic framework, crafted from metal connecting points and organic bridging ligands, can be used for the encapsulation of cisplatin [192]. Similarly, Reiter *et al*. reported cisplatin and its derivatives inclusion into nanoscale coordination polymers constructed from metal ion connectors and polydentate bridging ligands and finally stabilized against rapid dissolution in water by encapsulation in shells of amorphous silica [193]. Jain *et al*. developed hyaluronic acid-coupled chitosan nanoparticles bearing oxaliplatin encapsulated in Eudragit S100-coated pellets for effective delivery to colon tumors [194].

3.7. Curcumin

Curcumin (diferuloylmethane) is low molecular weight natural polyphenol isolated from turmeric (Curcuma longa), known for its anticarcinogenic (antiproliferative) properties and low intrinsic toxicity. Curcumin has been proved pharmacologically safe even at very high doses in many clinical studies and various animal models. However, it has extremely poor solubility in aqueous solution. Moreover, it quickly degrades in neutral and alkaline conditions with a half-life less than 10 min in PBS at pH 7.2, resulting in extremely low bioavailability after both vascular and oral administration [195]. To overcome these limitations, curcumin delivery by nanocarriers has been recently explored. Curcumin encapsulated in liposomes, micelles, polymeric nanoparticle, biodegradable microsphere, cyclodextrin, hydrogel nanoparticles or conjugated to water-soluble PAMAM dendrimers improved its water-solubility, stability, and thus bioavailability [196]. According to Bora *et al*., it is possible to use the composite nanoparticles consisting of three biocompatible polymers: alginate, chitosan, and pluronic [197]. The other nanocarrier for curcumin was synthesized from nonionic hydrophilic methoxy-PEG shell and hydrophobic palmitate core forming together the polymeric micelles [196]. Palmitate as a lipid hydrophobic moiety was also used in the combination with hydrophilic phthalimide derivative, which is a potent cancer chemotherapeutic candidate. This system is able to form the nanoparticles through a simple self-assembly process and then kill the cancer cells without any additional drug loading [198]. Tang *et al*. reported on the curcumin application as a co-monomer to make curcumin-containing polymers (polycurcumins) by polycondensation polymerization and on their *in vitro* and *in vivo* antitumor activities [195]. Another option is the use of nanoparticulate curcumin, which is more bioavailable and has a longer half-life than native curcumin as

revealed from pharmacokinetics study performed in mice by Mohanty *et al*. [199].

3.8. Geldanamycin

Geldanamycin is a benzoquinone ansamycin antibiotic that manifests anti-cancer activity through the inhibition of HSP90-chaperone function. The HSP90 (heat shock protein 90) molecular chaperone is expressed at high level in a wide variety of human cancers including melanoma, leukemia, and colon, prostate, lung, and breast cancer. Fukuyo *et al*. described the complicated molecular mechanism underlying the anti-cancer effect of HSP90 inhibition with respect to the recent progress in understanding HSP90 chaperone structure–function relationships, the identification of new HSP90 client proteins and the development of HSP90 inhibitors for clinical applications [200]. Won *et al*. reported on the development of self-assembled biodegradable nanoparticles based on recombinant human gelatin (rHG) modified with alpha-tocopheryl succinate (TOS) loaded with 17-AAG (17-allylamino-17-demethoxygeldanamycin) [201]. They concluded that the 17-AAG-loaded nanoparticles were nonimmunogenic and more efficient than free 17-AAG in manifesting an anticancer effect in the tumor model.

4. ADMINISTRATION ROUTES

The choice of a delivery route is driven by the various facts, such as i) patient acceptability, ii) the properties of the drug (e.g. its solubility), iii) access to a disease location, or iv) effectiveness in dealing with the specific disease. At present, there are several routes - peroral route, pulmonary delivery, transdermal delivery, parenteral routes including intravenous, intramuscular and subcutaneous, trans-tissue and local delivery systems, and gene delivery systems. The most important drug delivery route is the peroral one as it offers advantages of convenience and price availability of administration, and potential manufacturing cost savings [202].

Pulmonary delivery is also important and is realized in a variety of ways - *via* aerosols, metered dose inhaler systems (MDIs), powders (dry powder inhalers), and solutions (nebulizers); all of them may contain nanostructures such as liposomes, micelles, nanoparticles, and dendrimers. Aerosol products for pulmonary delivery comprise more than 30 % of the global drug delivery market. Research into lung delivery is driven by the potential for successful drug delivery, and by the promise of an effective delivery mechanism for gene therapy (for example, in cystic fibrosis treatment), as well as the need to replace chlorofluorocarbon propellants in MDIs. Pulmonary drug delivery offers both local targeting for the treatment of respiratory diseases and increasingly appears to be a viable option for the delivery of drugs systemically [203-208]. Transdermal drug delivery avoids problems such as gastrointestinal irritation, metabolism, variations in delivery rates and interference due to the presence of food. It is also suitable for unconscious patients. The technique is generally non-invasive and aesthetically acceptable, and can be used to provide local delivery over several days. Limitations include slow penetration rate, lack of dosage flexibility and/or precision, and a restriction to relatively low dosage drugs [176, 209-212].

Concerning the parenteral routes, the only nanosystems presently in the market (liposomes) are administered intravenously. Nanoscale drug carriers have a great potential for improving the delivery of drugs through nasal and sublingual routes, both of which avoid first-pass metabolism and for difficult access ocular, brain and intra-articular cavities. It has been possible to deliver peptides and vaccines systemically, using the nasal route, thanks to the association of the active drug macromolecules with nanoparticles. In addition, there is a possibility of improving the ocular bioavailability of drugs if administered in a colloidal drug carrier [213, 214].

Trans-tissue and local delivery systems require to be tightly fixed to resected tissue(s) during surgery. The aim is to produce an elevated pharmacological effect, while minimizing systemic, administration associated toxicity. Trans-tissue systems include: i) drug loaded gelatinous gels, which are formed *in situ* and adhere to resected tissue(s), releasing drugs, proteins or gene-encoding adenoviruses, ii) antibody fixed gelatinous gels (cytokine barrier) that form a barrier, which could prevent the permeation of cytokines into the target tissue, iii) cell-based delivery, which involves a gene transduced oral mucosal epithelial cell implanted sheet, and iv) device-directed delivery, a rechargeable drug infusion device that can be attached to the resected site [64].

Gene delivery is a challenging task in the treatment of genetic disorders. In the case of this approach, the plasmid DNA has to be introduced into the target cells, which should get transcribed and the genetic information should ultimately be translated into the corresponding protein. To achieve this goal, a number of hurdles are to be overcome by the gene delivery system. The transfection is affected by: i) targeting the delivery system to the target cell, ii) transport through the cell membrane, iii) uptake and degradation in the endolysosomes, and iv) intracellular trafficking of plasmid DNA to the nucleus [215-217].

5. CONCLUSION

Since visionary speech of Richard Feynman in 1959 starting the discussion about new field of research and development called nanotechnologies, numerous great steps in this field have been made. Nanotechnologies, the buzzword of the 21st century, find applications in very distinct areas of human research including both industrial and scientific branches. It is clear that medicinal applications are also included. This review has summarized the applications of various nanosizing strategies to carry drugs to the place of need. Since nanotechnology and nanomedicine are anticipated to be major drivers of personalized medicine, it is essential to focus the power of these technologies to enable personalized medicine through carrying the drugs (Fig. **7**). All strategies including nanocarriers, namely liposomes, micelles, PEG, PLGA, dendrimers, gold and magnetic nanoparticles [218], QDs [219], silica nanoparticles and CNTs [220] have advantages, which, in most cases, totally outweigh the disadvantages. Besides carrying drug itself, nanotechnologies have great potential in other medicinal branches such as non-invasive diagnostic, manufacturing nano-scale devices including nanorobots, drugs developing, etc. *In vivo* imaging is another area where nanotools and nanodevices are being developed. Using nanoparticle contrast agents, images such as ultrasound and MRI have a favorable distribution and improved contrast.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

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