Review

Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer

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Nanoscale drug delivery systems using liposomes and nanoparticles are emerging technologies for the rational delivery of chemotherapeutic drugs in the treatment of cancer. Their use offers improved pharmacokinetic properties, controlled and sustained release of drugs and, more importantly, lower systemic toxicity. The commercial availability of liposomal Doxil® and albumin-nanoparticle-based Abraxane® has focused attention on this innovative and exciting field. Recent advances in liposome technology offer better treatment of multi-drug-resistant cancers and lower cardiotoxicity. Nanoparticles offer increased precision in chemotherapeutic targeting of prostate cancer and new avenues for the treatment of breast cancer. Here we review current knowledge on the two technologies and their potential applications to cancer treatment.

Introduction

The application of innovative nanotechnologies to medicine – nanomedicine – has the potential to significantly benefit clinical practice, offering solutions to many of the current limitations in diagnosis, treatment and management of human disease. The diverse branches of nanomedicine include tissue regeneration [1], drug delivery [2] and imaging [3]. This review focuses on two nanotechnological drug delivery methods, liposomes and drug-conjugated nanoparticles.

Liposomes are closed spherical vesicles consisting of a lipid bilayer that encapsulates an aqueous phase in which drugs can be stored. The liposome diameter varies from 400 nm to 2.5 μm. Nanoparticles (NPs), which are particles ranging in size from 1 to 100 nm, exhibit unique physical and chemical properties that can be exploited for drug delivery by conjugation with drugs. Both these emerging nanoscale drug delivery systems can be used to improve current treatment regimens (Box 1).

High drug toxicity is a barrier to treatment because side effects limit the drug dosage that can be administered. This is best exemplified by cytotoxic cancer drugs. Although very effective *in vitro*, in human clinical use the drugs act indiscriminately on both cancerous and healthy tissues. Side effects can be both serious and unpleasant and range from nausea and hair loss to neuropathies, neutropenia and kidney failure. Therefore, drug non-specificity limits efficacy [4]. Box 2 details recent drugs and diseases under investigation for the use of nanoscale drug delivery.

This review outlines recent developments in the use of liposomes and NPs in the field of drug delivery for the treatment of cancer. An understanding of these new technologies is needed for the advancement of chemotherapy with higher efficacy and lower toxicity.

Advantages of nanoscale drug delivery systems

The ideal nanoscale drug delivery system ensures that the conjugated or bound drug–carrier complex arrives and acts preferentially at the selected target. Targeting of the drug–nanocarrier complex can be active, whereby the complex incorporates a ligand specific for the receptor or epitope of the target tissue (Table 1). In passive targeting, complexes diffuse and accumulate at sites with excessively leaky microvasculature, such as tumours and inflamed tissues, with normal endothelium being much less permeable. Subsequent extravasation of complexes takes place either via transcytosis, whereby macromolecules are internalized from the blood at points of invagination of the cell membrane, or paracellularly, via diffusion through the tight junctions of endothelial cells. Particularly in cancers, an imbalance in factors that regulate angiogenesis, such as overexpression of vascular endothelial growth factor (VEGF), results in both increased vascular permeability and chaotic tumour-vessel architecture. In combination, these effects cause enhanced permeation and retention (EPR) [5], resulting in high local drug concentrations.

Key properties of any nanomaterial used in drug delivery are its biocompatibility and biodegradability, so that the unloaded carrier is degraded or metabolized into non-toxic components and cleared through the circulation. Materials are cleared according to size. Small particles (0–30 nm) are rapidly cleared by renal excretion. Nanocarriers >30 nm are cleared by the mononuclear phagocytic system (MPS), consisting of macrophages located in the liver (Kupffer cells) and the spleen [6], which act as phagocytotic scavengers. Clearance is also dependent on endothelial fenestral size [6]. Fenestrae are highly variable, so it is difficult to determine the efficacy and toxicity of nanomedicines in different individuals because age, sex and genetics influence their rate of clearance [4]. Whether nanocarriers are taken up by macrophages depends on opsonization by the innate immune system [7]. Opsonins,

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Box 1. Goals of a nanoscale drug delivery system

(i) Targeting, to increase the drug concentration at desired sites of action and reduce systemic levels of the drug and its toxic sequelae in healthy tissues.
(ii) Improved solubility, to facilitate parenteral drug administration.
(iii) Constant rate of drug delivery, resulting in zero-order release kinetics to maintain a constant therapeutic dose at the site of action [9].
(iv) Reduced clearance, to increase the drug half-life.
(v) Increased drug stability, to reduce degradation and maximize drug action.
(vi) Drug delivery across the blood–brain barrier (BBB) [58] and blood–cochlear barrier [59].

molecules that bind to foreign materials and enhance phagocytosis, include IgG and IgA antibodies, the complement cascade system and mannose-binding lectin [8]. Therefore, the surface properties of nanocarriers can significantly affect the rate of clearance by the MPS. A useful method for evading opsonization of large narrow carriers was developed in Rutgers University in the 1960s [9]: in a process called PEGylation, a polymer, poly(ethylene glycol) (PEG; $[CH_2CH_2O]_n$), is conjugated to the drug carrier.

Overall, use of ligand–drug–nanocarrier complexes improves the drug therapeutic index according to Eq. (1). The high selectivity and specificity of the complex, increases the amount of drug delivered to the target tissue and decreases the amount at unwanted sites. Therefore, less systemic drug needs to be administered to ensure a sufficient concentration at the site of action and the minimum efficacious dose is also lower. In addition, because less drug is present at unwanted sites, the maximum non-toxic is higher. The overall effect is a drastic decrease in toxicity and adverse side effects [10].

$$\text{Therapeutic index} = \frac{\text{Maximum non-toxic dose}}{\text{Minimum effective dose}}. \quad (1)$$

Nanoscale drug delivery systems

Liposomes

The liposome bilayer can be composed of either synthetic or natural phospholipids. The predominant physical and chemical properties of a liposome are based on the net properties of the constituent phospholipids [11], including permeability, charge density and steric hindrance. The lipid bilayer closes in on itself due to interactions between water molecules and the hydrophobic phosphate groups of the phospholipids. This process of liposome formation is spontaneous because the amphiphilic phospholipids self-associate into bilayers. Drug loading into liposomes can be achieved through (i) liposome formation in an aqueous solution saturated with soluble drug; (ii) the use of organic solvents and solvent exchange mechanisms; (iii) the use of lipophilic drugs; and (iv) pH gradient methods [12] (Figure 1).

Liposomes generally reach their site of action by extravasation into the interstitial space from the bloodstream. Liposomes can target specific tissues through both active and passive targeting strategies (Figure 2). This is because liposomes can easily be manipulated by adding additional molecules to the outer surface of the lipid bilayer. Because liposomes are of the order of 400 nm in size, they are rapidly cleared by the MPS system. Reducing opsonization of liposomes by PEGylation therefore reduces clearance by the MPS, increasing the circulation half-life. Opsonization presents such a problem to the development of therapeutically useful liposomes that nearly all research reported in the literature involves PEG-coated or PEGylated liposomes.

Liposomal formulations of anticancer drugs have already been approved for human use. Doxil® is a liposomal formulation of the anthracycline drug doxorubicin used to treat cancer in AIDS-related Kaposi sarcoma and multiple myeloma [13]. Its advantages over free doxorubicin are greater efficacy and lower cardiotoxicity. These advantages are attributed to passive targeting of tumours, due to leaky

Box 2. Potential therapeutic opportunities for nanoscale drug delivery in diseases other than cancer

Nanocarrier	Drug	Disease	Advantages
SLNs [60]	Insulin	Diabetes mellitus	Pulmonary administration possible; an inhaler or nebulizer replaces a daily regimen of subcutaneous injections, increasing patient satisfaction and compliance
Liposomes [61]	Vasoactive intestinal peptide (VIP)	Hypertension	Potential new treatment for hypertension using VIP, which is limited by rapid degradation in blood by first-pass hepatic circulation
Liposomes (Ambisome®) [62]	Amphotericin B	Fungal infections	Reduced renal toxicity and greater efficacy in treating fungal infections; also used to treat other parasitic infections
Gold nanoparticles [63]	Ciprofloxcain	Bacterial infections such as urinary tract infections, cystitis, sinusitis and respiratory tract infections	Sustained release over a number of hours and greater local concentrations of the free drug at sites of pathology because of the permeation and retention effect
PLGA nanoparticles [64]	Rifampicin	Tuberculosis	Sustained release over a period of days, increasing patient compliance because medication can be taken weekly instead of daily over a period of 6 months
PLGA nanoparticles [65]	Benzocaine	Pain relief	Parental administration possible; only a single dose is required for a prolonged effect
SLNs [66]	Clozapine	Schizophrenia	Higher clozapine concentrations across the blood–brain barrier compared to clozapine solution

Table 1. Typical examples of active targeting with drug delivery systems[a].

Ligand	Receptor/target	Study findings
Anti-CD74 antibody, LL1 [49]	CD74 receptor	Ligand covalently attached to liposomes; selective for malignant B lymphoma cells
TfR-targeting peptide HAIYPRH [50]	TfR	Conjugation to the TfR-binding peptide significantly improves the anti-cancer potency and selectivity of the anti-cancer drug artemisinin
Folate [51]	Folate receptor (FR)	FR is overexpressed on cancer cells Folate has been conjugated on liposomes loaded with doxorubicin for targeting of cancer an on NPs for targeted paclitaxel delivery
mBAFF [52]	BAFF receptor	BAFF is the usual endogenous ligand for the BAFF receptor; mBAFF is a soluble BAFF mutant in which amino acids 217–224 are replaced by two glycine residues that can bind to BAFF receptors PEGylated liposomes developed with mBAFF as a targeting ligand target certain B lymphoma cells *in vitro*
Hyaluronic acid [53]	Hyaluronan receptors (HR)	HT-29 cancer cells overexpress HR Hyaluronic acid incorporated in chitosan NPs loaded with the anti-cancer drug 5-flurouracil exhibited higher cytotoxicity *in vitro*
Galactose [54]	ASGP receptors	ASGP receptors are overexpressed on hepatoma cells Dextran-based polymeric micelles were used to target liver cancer *in vivo* with superior results

[a]AGIP, amyloid growth inhibitory peptide; ASGP, asialo glycoprotein; mBAFF, mutant B cell activating factor belonging to the TNF family; SAP, sweet arrow peptide; TfR, transferrin receptor.

tumour vasculature [14] and the EPR effect, and to lower concentrations of free doxorubicin at healthy tissue sites. There is evidence that liposomal Doxil® is metabolized by leukaemia cells via a different mechanism than that for free doxorubicin, which might explain the improved efficacy and lower toxicity. Furthermore, Doxil® is under clinical trial for the treatment of breast cancer.

One of the most interesting developments in this field is the potential of liposomes to combat the increasing problem of multidrug resistance (MDR) acquired by cancers, which drastically reduces chemotherapeutic efficacy. Proposed mechanisms underlying MDR at the cellular level include: (i) increased metabolism of drugs due to increased enzyme expression, especially of glutathione S-transferase; (ii) drug transporters and efflux proteins [15]; and (iii) point mutations in proteins that are therapeutic or drug targets. Ogawara *et al.* recently investigated the effect of PEG liposomal doxorubicin (Doxil®) in a male mouse tumour model inoculated with either colon cancer (C26) cells or their doxorubicin-resistant (MDR) subclone, which overexpresses P-gp efflux pumps [16]. The results showed that PEG liposomal doxorubicin had anti-tumour effects on both doxorubicin-resistant and non-doxorubicin-resistant C26 cells. With increasing incidence of resistance to chemotherapy, the use of liposomes offers effective treatment without the need for the costly discovery of new chemotherapeutic drugs because current drugs can be reformulated.

To date, no specific *in vivo* study has compared the efficacy of liposomes to that of other nanoparticle delivery systems; therefore, we cannot comment on the relative efficacy of liposomes.

Liposomes are firmly established with the success of Doxil®, and new liposomal formulations of other anticancer drugs are now being intensively explored to improve chemotherapy outcomes and reduce toxicity.

Solid lipid NPs

Solid lipid NPs (SLNs), also referred to as lipospheres or solid lipid nanospheres, are solid lipids at human physiological temperature (37 °C) and have a diameter of

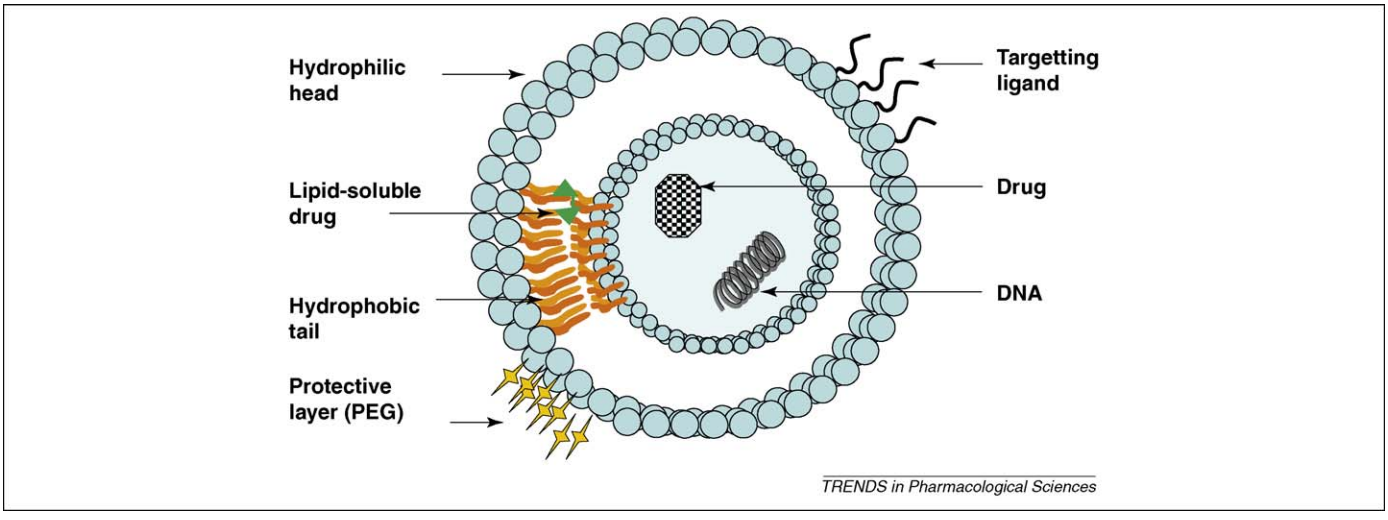

Figure 1. Diagram of a bilaminar liposome. The hydrophobic region traps drugs in the central core when the liposomes are prepared. The outer surface can be functionalized with ligands for active targeting or PEGylated. Liposomes can vary in the number of lipid bilayers they possess and can be classified into three categories: (i) multilamellar vesicles, (ii) large unilamellar vesicles and (iii) small unilamellar vesicles.

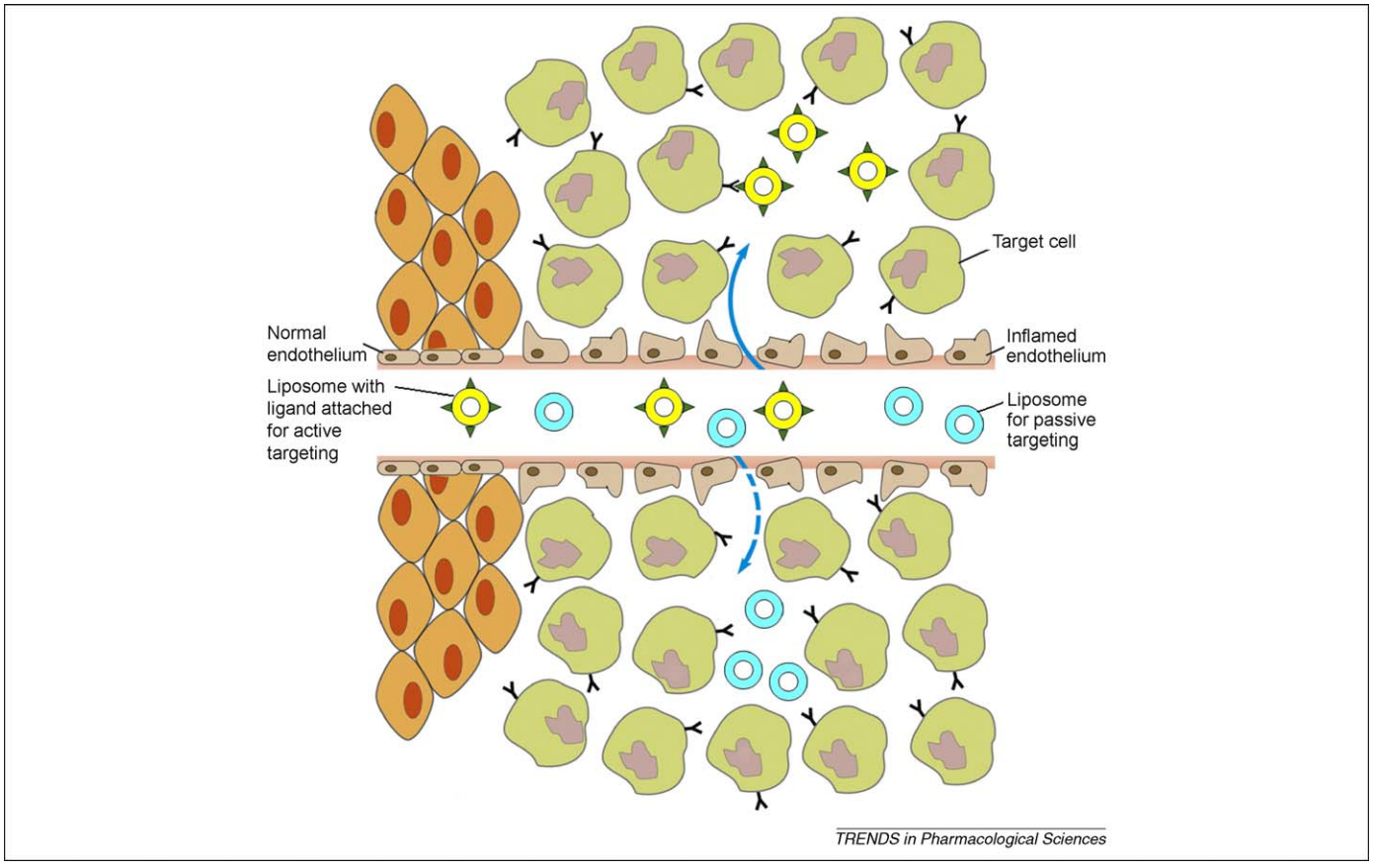

Figure 2. Active and passive targeting of cells for drug targeting using liposomes. At sites of pathology where the endothelium layer is inflamed, mediators such as bradykinin, vascular endothelium growth factor and prostaglandins increase the endothelial permeability. Underlying pathology includes cancer, rheumatoid arthritis and infection. Liposomes extravasate through the gaps between cells and enter the interstitial fluid. Active targeting is achieved by conjugating ligands to the liposome that bind to a specific target cell receptor, leading to internalization or release of the drug. Passive targeting can be mediated by internalization or local high-concentration release of the drug. Adapted from Ref. [32].

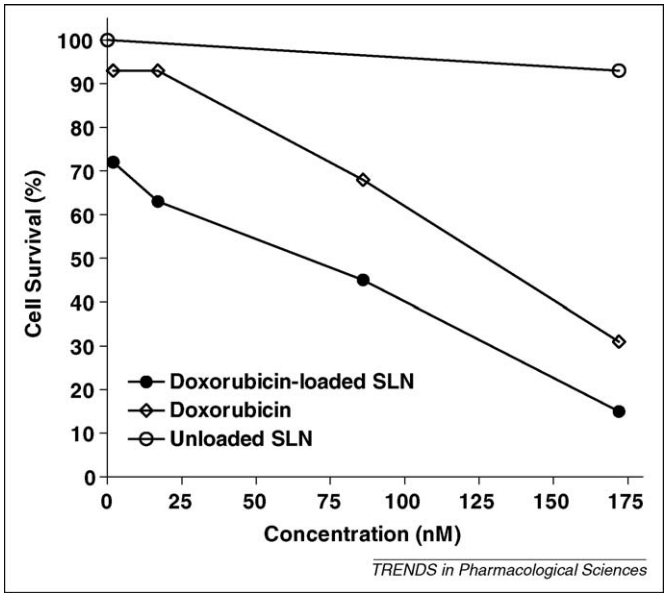

Figure 3. Benefits of SLNs in doxorubicin delivery. The cytotoxicity of free doxorubicin, doxorubicin-loaded SLNs and unloaded SLNs at different concentrations towards HT-29 colorectal cancer cells after 72-h exposure is shown. Doxorubicin-loaded SLNs showed the highest toxicity, offering more potent treatment than conventional free doxorubicin. Unloaded SLNs did not induce any significant toxicity, which confirms that they are a safe carrier *in vitro* [19].

50–1000 nm. They can be formed from a range of lipids, including mono-, di- and triglycerides, fatty acids, waxes and combinations thereof. SLNs are produced by replacing the liquid lipid (oil) of an oil-in-water emulsion by a solid lipid and many commercially viable methods are available for large-scale production. SLNs are biodegradable and biocompatible and can be used in humans because of their low toxicity [17]. SLNs must be stabilized by surfactants to form administrable emulsions [18].

SLNs form a strongly lipophilic matrix into which drugs can be loaded for subsequent release. The principal factors affecting drug loading into the SLN matrix are: (i) the solubility of the drug in lipid (the drug must be lipophilic); (ii) the chemical and physical properties of the lipid or mixture of lipids; (iii) the crystalline characteristics of the lipid(s) at biological temperature; and (iv) the polymorphic form of the lipid(s) used. Use of a heterogeneous lipid mixture promotes an imperfect crystalline structure with larger gaps for superior drug loading.

SLNs have been investigated for the delivery of various anticancer drugs, with promising results in preclinical mouse trials specifically showing that SLNs might help to overcome MDR in cancers [17]. Serpe *et al.*, using colon cancer cells *in vitro*, demonstrated the benefits of SLNs in the delivery of doxorubicin (Figure 3), cholesteryl butyrate and paclitaxel [19].

Table 2. Representative examples of studies using drug-carrying nanoparticles[a]

NP polymer	Drug	Study findings
PLGA [55]	Doxorubicin	A single intravenous injection of doxorubicin conjugated to PLGA NP exhibited tumour suppression comparable to that by daily injection of free doxorubicin over 12 days; thus, the NP formulation was much more potent and longer-lasting than conventional free doxorubicin
PLGA [51]	Dexamethasone	A single administration produced at least 14 days of sustained drug release; clinical application in suppressing glial cell proliferation on implanted electrodes for neurophysiological investigations into neural activity
PLA [56]	Thyrotropin-releasing hormone	Intranasal delivery through olfactory neurons to reach the brain; tested for an anticonvulsant in an animal seizure model; clinical application of peptide delivery to the brain without crossing the blood–brain barrier
PLA–TPGS/MMT NP [57]	Docetaxel	Much greater cytotoxic potency to cancer cells than Taxotere® (current clinical form of docetaxel)

[a]NP, nanoparticle; PLA–TPGS/MMT NP, poly(lactide)–D-α-tocopheryl poly(ethylene glycol) 1000 succinate copolymer incorporated in montmorillonite medical clay.

In an exciting development, mitoxantrone, a topoisomerase inhibitor that blocks DNA replication, was loaded into SLNs and used *in vivo* as a local injection to treat breast cancer and lymph node metastases in mice [20]. The results revealed a nearly threefold reduction in lymph node size compared to free mitoxantrone, which is a significant improvement on the existing treatment.

SLNs offer an alternative platform for drug delivery in cancer. However, more *in vivo* studies are required before they can be translated to human treatment.

Polymer-based NPs

Polymeric NPs have been extensively investigated as drug nanocarriers. As a class of molecule, their designs are very similar, with a polymeric backbone – usually formed from a biodegradable monomer based on a simple organic molecule that is biocompatible – and functional moieties for active targeting intercalated into the structure [21]. Drug loading is achieved either by (i) entrapment of an aqueous drug phase using the polymer to form nanoscale structures such as cages and capsules [21,22] or (ii) chemical linking of the drug molecules to the polymer backbone by means of a simple ester or amide bond that can be hydrolyzed *in vivo*. More complex polymeric NPs use polar groups to create hydrophobic and hydrophilic regions enabling the drug to adsorb onto the NP and facilitate delivery to the target site.

The most widely researched synthetic polymers include polylactide (PLA) [23], poly(D,L-lactide–co-glycolide) (PLGA) [24] and PEG [25]. All three polymers are hydrolyzed *in vivo* and are biodegradable. Other polymers based on biological polysaccharides have been extensively investigated, including chitosan, cyclodextrin and dextrans [26]. Different polymers can be combined to form co-polymers. PLA-block-PEG co-polymers harness the properties of both polymers, especially the anti-opsonization of PEG [24]. Ligands can be attached to the NP to facilitate active targeting. Ligands can be intercalated into the structure either by direct covalent linkage to the polymeric backbone or through the use of biologically inert spacer groups [27].

Ligands for active targeting of cancer are used to exploit any specific antigens expressed by cancer cells. RNA A10 aptamers specific for the prostrate-specific membrane antigen have been successfully conjugated onto PLA-block-PEG co-polymers, which exhibited increased drug delivery to prostate tumour cells compared to non-targeting NPs [27]. This is a promising development and might offer better non-surgical treatment for prostate cancer patients.

Current paclitaxel formulations (Taxol®), a drug for breast cancer chemotherapy, use the organic solvent Cremophor EL®, which can elicit severe hypersensitivity reactions. PEGylated PLGA copolymer NPs showed an encapsulation efficiency of 70% for paclitaxel and induced a similar level of apoptotic cell death as that observed for Taxol® when tested on HeLa cancer cells [28]. Significantly, the PEGylated PLGA copolymer showed no toxicity and therefore an effective formulation of paclitaxel can be produced without the adverse effects associated with Cremophor EL® [28]. This offers an alternative treatment to those who are sensitive to Cremophor EL® without compromising on chemotherapeutic potency.

Cisplatin, another anticancer agent, has been loaded into copolymer PLGA–methoxy-PEG (PLGA–mPEG) NPs [29]. *In vitro* testing revealed that cisplatin-loaded PLGA–mPEG NPs passively targeted LNCaP prostate cancer cells. Cisplatin-loaded NPs evoked less cytotoxicity than free cisplatin solution, but their passive targeting reduced systemic toxicity. Fluorescence microscopy revealed that cisplatin-loaded NP uptake occurred via internalization. An *in vivo* mouse model revealed that cisplatin blood levels were prolonged and sustained at therapeutic concentrations after intravenous administration. Table 2 lists some other salient studies in this field.

Polymeric NPs are still in the preclinical phase of development but have potential for the targeted delivery of anticancer drugs owing to the ease with which ligands can be attached.

Gold NPs

Gold NPs consist of a core of gold atoms that can be functionalized by addition of a monolayer of moieties containing a thiol (SH) group [30]. Examples of these moieties include ligands for active targeting of the gold NP, such as masked phosphonioalkyl selenoates [31], peptides and glyconanoparticles. Gold NPs can be synthesized using $NaBH_4$ to reduce $AuCl_4^-$ salts in the presence of thiol-containing moieties that subsequently form a monolayer around the core gold atom, depending on the stoichiometric gold/thiol ratio (Figure 4) [32]. Synthesized NPs have a diameter of 1–150 nm. Further NP modification can be carried out using a place exchange reaction, in which thiol-containing moieties are swapped. In this way, a single

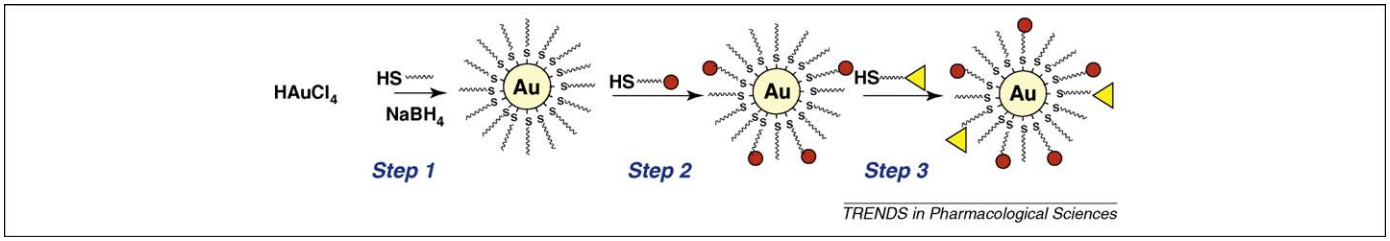

Figure 4. Synthesis of gold nanoparticles. In step 1, the Schiffrin reaction, $AuCl_4^-$ is reduced by $NaBH_4$ in the presence of functional moieties with thiol groups. In step 2, the Murray reaction, different functional moieties with thiol groups (represented by different colours) can be swapped in a place-exchange reaction [32]. Step 3 involves further addition of a different thiol ligand.

gold NP core can be functionalized with many different groups for targeting, stability, evasion of host defences and drug delivery [32].

Studies have confirmed that gold NPs are non-toxic at the cellular level in a number of human cell lines [33]. Studies in mice using gold NPs as an imaging agent revealed no evidence of toxicity over 30 days [34]. A pioneering study demonstrated that PEGylated gold NPs (10–30 nm) are unable to cross the human placenta within 6 h, which could be used to restrict drug delivery to just the mother while preventing teratogenic effects on the foetus [35].

Drug delivery using gold NPs is still in its infancy, although much more progress has been made in DNA delivery for gene therapy [36] and in imaging [37]. Gold NPs can be synthesized and functionalized with anticancer drugs such as paclitaxel and 6-mercaptopurine (6-MP) [38]. Gold NPs co-administered with paclitaxel show enhanced anti-proliferation effects on tumours. It is thought that gold NPs disrupt cell adhesion [39]. The anti-leukaemia drug 6-MP bound to gold NPs exhibits greater *in vitro* toxicity against leukaemia than free 6-MP, even though gold NPs had no anti-leukaemia activity in control studies.

The most novel development for gold NPs is the use of intracellular glutathione as a trigger for drug release [40]. The higher glutathione levels found in cancerous and pre-cancerous cells could thus be exploited in targeting intracellular release of chemotherapy drugs [41].

Although drug delivery using gold NPs is still evolving, there is potential for developing multifunctional particles for imaging, drug and gene delivery systems for application in cancer.

Albumin NPs

Albumin, a plasma protein with a molecular weight of 66 kDa, has been extensively investigated as a drug carrier, with promising results. It is soluble in both water and ethanol, two viable solvents for intravenous administration. Because albumin is found in the circulating plasma of the human body at concentrations of 50 g/L of serum, it is non-toxic and well tolerated by the immune system. Albumin has favourable pharmacokinetics owing to its long half-life in circulating plasma, which makes it particularly attractive as a drug carrier for passive targeting [42]. Albumin can be derived from human plasma and blood products. Alternatively, recombinant human serum albumin can be produced in genetically engineered yeast cells [42]. Albumin NPs are prepared by desolvation or coacervation.

Abraxane®, also known as nab-paclitaxel, is the first drug based on an albumin NP approved for human use by the US Food and Drug Administration. The chemotherapy drug paclitaxel is bound to 130-nm human albumin NPs. Abraxane® has advantages over free paclitaxel in terms of its longer circulation half-life and lack of the hypersensitivity-inducing Cremophor EL® solvent [43]. Clinical trials have confirmed the efficacy of Abraxane® in the treatment of metastatic breast cancer, for which it is routinely used [44]. In addition, Abraxane® is currently being investigated with other taxanes in the treatment of hormone refractory prostate cancer [44]. Albumin is transported across the endothelium into the extravascular space by transcytosis via caveolae, initiated by the albumin receptor gp60 [45]. Tumour tissues have a high metabolic demand and actively transport plasma proteins into their cells for anabolic processes. It has been proposed that this mechanism would explain why Abraxane® targets and preferentially accumulates in cancer tissues *in vivo* [46] via the excessive vascular network associated with cancers [44]. There is also speculation that Abraxane® is transported into tumour cells by secreted protein acidic rich in cysteine (SPARC) or osteonectin [44].

Albumin–PEG–PLA NPs cross the blood–brain barrier [47] and conjugation of apolipoproteins can facilitate transcytosis [48]. These findings open new avenues for the use of albumin NPs as a carrier for drug delivery to the brain not only for cancer treatment, but also for a wide range of central nervous system diseases.

Conclusions and future direction

Liposomes and NPs are promising candidates for the development of drug delivery systems. Early experimental evidence, both clinically and preclinically, shows great potential for the widespread adoption of liposomes and NPs in cancer treatment. Their attractive properties include biocompatibility, low toxicity, lower clearance rates, the ability to target specific tissues and controlled release of drugs. They offer numerous advantages over conventional chemotherapy using free drug treatment, as evidenced by the approval of Abraxane® and Doxil®. Both of these nanomaterial-based formulations of existing drugs offer better pharmacokinetic properties and lower systemic toxicity of the chemotherapeutic drugs that they deliver.

However, the full potential of these emerging technologies has not yet been fully realized. The toxicology of nanomaterials in humans still needs to be fully studied and evaluated. Studies so far have been small and limited to short-term exposure; few have looked at the wider

impact. Investigation into so-called nanotoxicity should focus on long-term exposure in humans, animals and the environment. Further *in vivo* studies are needed to determine the efficacy of these new drug formulations, culminating in phase I trials. The reproducibility of batches of drug formulations such as liposomes and NPs also needs to be refined.

Liposomes and NPs are just beginning to make an impact in chemotherapy owing to the dual drive to reduce the toxicity and side effects of existing treatments and increase efficacy by selective targeting of tumours.

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