

Nanoparticles As Platforms For Targeted Drug Delivery System In Cancer Therapy

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Abstract

Over Recent years advancement in nanoparticles drug delivery is widely expected to change the landscape of pharmaceutical and biotechnology industries for the foreseeable future [123]. The pipelines of pharmaceutical companies are believed to be drying up in many cases, and a number of blockbuster drugs will come off patent in the near-term [4]. Using nanoparticles, it may be possible to achieve (1) improved delivery of poorly water-soluble drugs by delivering drug in small particle size increase the total surface area of the drugs allowing faster dissolution in blood stream.

INTRODUCTION

Over Recent years advancement in nanoparticles drug delivery is widely expected to change the landscape of pharmaceutical and biotechnology industries for the foreseeable future [123]. The pipelines of pharmaceutical companies are believed to be drying up in many cases, and a number of blockbuster drugs will come off patent in the near-term [4]. Using nanoparticles, it may be possible to achieve (1) improved delivery of poorly water-soluble drugs by delivering drug in small particle size increase the total surface area of the drugs allowing faster dissolution in blood stream. Faster the dissolution translates in to faster absorption by human body (2) targeted delivery of drugs in a cell- or tissue-specific manner; (3) transcytosis of drugs across tight epithelial and endothelial barriers; (4) delivery of large macromolecule drugs to intracellular sites of action; (5) co-delivery of two or more drugs or therapeutic modality for combination therapy; (6) visualization of sites of drug delivery by combining therapeutic agents with imaging modalities; and (7) real-time read on the in vivo efficacy of a therapeutic agent [5]. A nanoparticle has emerged as a promising strategy for the efficient delivery of drugs used in the treatment of cancer by avoiding the reticuloendothelial system, utilizing the enhanced permeability and retention effect and tumor-specific targeting [3]. These carriers are designed in such a way that they are independent in the environments and selective at the pharmacological site. The formation of nanoparticle and physiochemical parameters such as pH, monomer concentration, ionic strength as well as surface charge, particle size and molecular weight are

important for drug delivery. Further, these nanoparticles have the capability to reverse multidrug resistance a major problem in chemotherapy. Well-established therapies commonly employed in cancer treatment include surgery, Chemotherapy, immunotherapy, and radiotherapy [6].

VARIOUS APPROACHES FOR NANOPARTICLES DRUG DELIVERY IN CANCER THERAPY

The challenge of modern drug therapy is the optimization of the pharmacological action of drug, coupled with the reduction of their toxic side effect in vivo. In cancer treatment and detection, nanoparticles serve many targeted functions in chemotherapy, thermotherapy, radiotherapy, photodynamic therapy, immunotherapy and anti angiogenesis.

PHOTO THERMAL ABLATION THERAPY

In general, thermal ablation therapy refers to hyperthermia as well as thermotherapy. Hyperthermia therapy is based on the fact that tumour cells are more sensitive to temperature increase than normal tissue cells. It involves tumour heating to temperatures between 41-45 °C inducing almost reversible damage to cells and tissues. For thermal ablation therapy higher temperatures are applied, i.e. ranging from 50 °C to 70 °C, leading to the destruction of pathologically degenerated cells. In case of successful treatment, either the tumour disappears, diminishes, or at least stops growing; Hyperthermia therapy in combination with immunotherapy could also offer feasible treatment of advanced

malignancies. Heating methods can use energy sources based on radiofrequency electric fields, magnetic fields, microwave, ultrasound, and optical applicators. In clinical settings radiofrequency electric field-induced heating is most commonly used, although application is still hampered due to factors of such as heterogeneity of tissue electrical conductivities, position of electrodes, adhesion of electrodes at uneven sites, and tumour size which make selective heating very difficult [78].

PHOTO-THERMAL ABLATION THERAPY USING SILICA NANOSHELLS

Nanoshells can be used for photo-thermal ablation of tumour tissue as demonstrated both human breast carcinoma cells in vitro and in a murine model in vivo [9]. Nanoshells are layered, spherical nanoparticles consisting of dielectric silica (SiO_2) core coated with a thin metal shell. These ceramic-based nanoparticles have a diameter of 100-200 nm and the coating is 10 nm thick. By manipulating the size of the silica core and the thickness of the gold shell, the plasmon resonance response can be tuned. This is a phenomenon whereby light induces collective oscillations of conductive metal electrons at the nanoshell surface. The nanoshell's plasmon resonance, in turn, determines the absorbing and scattering properties of the particle, so that the nanoshell can be selectively activated. Gold usually absorbs light from the visible to ultraviolet part of the electromagnetic spectrum, which can burn tissue. However, electromagnetic interactions between the gold nanoparticles change the property of the metal, making it absorb light from the near-infrared, which can easily penetrate several centimetres of human tissue without harming it. In the murine model poly (ethylene glycol)-passivated gold-coated silica nanoshells were injected interstitially ~5 mm into the tumour volume (tumour size 3-5.5 mm). Poly (ethylene glycol) is used to increase circulation time as well as to reduce non-specific attachment or uptake. The blood vessels inside tumours develop poorly, allowing the nanoshells to leak out and accumulate inside tumours. Six hours after the injections an external laser source of near infrared light is applied through the skin for 3-7 minutes. The gold nanoparticles readily absorb the energy and turn it into heat resulting in an average temperature increase of ~37 °C which induces irreversible cancerous tissue damage. The heating is localised and does not affect healthy tissue adjacent to the tumour. The mice remain cancer-free after the treatment, whereas growth of tumours in the control group, i.e. no treatment and sham group, continues rapidly. It is also possible to attach biological markers, such as antibodies and

proteins, to the nanoshells, in order to direct them to their target tissues [10]. This non-invasive localised thermal ablation technology can be used to replace or supplement chemotherapy and surgery and is licensed to the company Nanospectra Biosciences, Inc. Houston, Texas, USA [910].

The advantage of using smaller particles is that they can be inserted into any part of the human body to treat cancer cells in their infancy. The biocompatibility of silica and gold at the nanoscale has yet to be investigated, as gold particles become very reactive when they are reduced to a very small size [11].

PHOTO-THERMAL ABLATION THERAPY USING CARBON NANOTUBES

Functionalised Single walled carbon nanotubes (SWCNTs) can achieve near-infrared light-triggered selective tumour cell destruction without harming normal cells in vitro. Folate-functionalised SWCNTs are internalised inside HeLa tumour cells as the surface of these cancer cells is covered with abundant folate receptors. Continuous near-infrared light radiation by a laser for 2 min causes excessive local heating and triggers cell death. Compared to the optical properties of other nanomaterials, such as gold-coated silica nanoshells, SWCNTs are favourable with lower laser power and shorter radiation times necessary for effective tumour cell destruction. It should be noted that pulsed laser radiation causes delivery of DNA-SWCNT conjugates without destroying cells. Hence, the optical and transporting properties of SWCNTs could lead to new classes of novel nanomaterials for drug delivery and cancer therapy.[91213]

MAGNETIC NANOPARTICLES FOR CANCER THERAPY

Another approach uses magnetic fields in conjunction with magnetic nanoparticles, such as superparamagnetic iron oxide nanoparticles, paramagnetic copper-nickel alloy nanoparticles, or magnetite (Fe_3O_4) cationic liposomes. These nanoparticles remain silent until activated in the treatment zone by the application of a localised magnetic field. Once an alternating magnetic field is applied heat is generated within the nanoparticles providing selective heating to cancerous tissues loaded with the thermal agent only. The amount of heat generated depends on the type of particle, as well as the frequency and strength of the applied magnetic field.[141516].

MagForce Nanotechnologies GmbH, Berlin, Germany has developed an AC magnetic field applicator (MFH® 300F) in

conjunction with MagForce® nanoparticles for hyperthermia treatment of brain tumours, also known as “magnetic fluid hyperthermia”. The magnetic fluid consists of superparamagnetic iron oxide nanoparticles in aqueous solution administered by stereotactic navigation-based injection into brain tumour tissue. The iron oxide is covered by an aminosilane type shell. Due to the universal design of the magnetic applicator, it can be used for hyperthermia as well as thermal ablation treatment of malignancies in any part of the human body. Several clinical investigations, i.e. feasibility and efficacy studies, are being performed at the Charité University Hospital in Berlin including patients with tumours in different body parts, i.e. brain and prostate. The entire treatment takes approximately 2 hours, including the therapy with 60 minutes, heating periods and time for preparing the patient.^[17].

A more advanced approach is currently being developed by Triton Bio Systems, Inc. Chelmsford, Massachusetts, USA. A non-invasive targeted therapy for the treatment of solid breast tumours, referred to as the Targeted Nano-Therapeutics™ System, consists of polymer-coated superparamagnetic iron oxide nanoparticles bound to monoclonal antibodies about 40 nm long. This “bioprobe” is injected into the blood circulation, where the antibodies detect the unique chemical signature of cancer cells and bind to their membrane receptors.

PHOTODYNAMIC THERAPY

Photodynamic therapy is an emerging treatment modality where a light-sensitive molecule or photosensitiser exposed to visible or near-infrared light induces cytotoxic effects in the presence of oxygen. When photosensitisers are irradiated, the excited molecules can transfer their energy to molecular oxygen. Two types of photodynamic reactions are observed. First, reactions in which electron of hydrogen-transfer occurs producing reactive oxygen species (ROS) or free radicals, such as superoxide (O_2^-), hydrogen peroxide, hydroxyl and hydroperoxyl radicals. Second, reactions in which an electron spin exchange occurs between the photosensitiser and triplet oxygen (3O_2), resulting in the production of cytotoxic singlet oxygen (1O_2). Singlet oxygen is accepted as the main mediator of photocytotoxicity in photodynamic therapy, causing irreversible cell damage by oxidation and degradation of intracellular biomembrane structures, but with minimal systemic toxicity. Photodynamic therapy can be used to treat a variety of oncological, cardiovascular, dermatological, ophthalmic, and immunological disorders. Compared with conventional

surgery, the approach is non-invasive, enables accurate targeting, repeated administration without total-dose limitations associated with radiotherapy, and results in little or no scarring after healing.^[18].

A common problem among many first and second-generation photosensitisers, e.g. Photofrin® I, Photofrin® II (Axcan Pharma Inc., Mont-Saint-Hilaire, Quebec, Canada), methylene blue, porphyrin, phthalocyanine, is the difficulty in preparing appropriate pharmaceutical formulations. The most potent photosensitisers are hydrophobic and poorly water-soluble and therefore difficult to administer as such especially when intravenous injection is needed. This issue calls for the use of advanced delivery systems and different strategies have been investigated, which mainly include polymer-photosensitiser conjugation as well as encapsulation of the photosensitiser in colloidal carriers such as liposomes, oil dispersions, and polymeric particles. Recently, nanoparticles have received increasing attention as potential delivery systems for photodynamic therapy agents.^[19]

QUANTUM DOTS AS PHOTOSENSITISERS AND CARRIERS

Quantum dots offer several advantages as potential delivery systems for photosensitisers. The optical properties of this nanomaterial can be tuned to absorb and emit in the near-infrared region of the spectrum by changing their size and composition. Light of low intensity can be used to penetrate tissue several centimetres allowing access to deep-seated tumours. Importantly, the surface coating of quantum dots can be functionalised to make them more water soluble and biocompatible, which facilitates systemic delivery ^[20].

Quantum dots can act as photosensitiser alone generating reactive singlet oxygen as well as promote the effect of classical photosensitisers linked to quantum dots. Close steric proximity between quantum dot and photosensitisers ensures a highly efficient fluorescence resonance energy transfer (FRET) and increased photosensitising power. The cadmium selenide (CdSe) quantum dot-based FRET to facilitate excitation of photosensitisers, such as phthalocyanines, has been demonstrated in oxygen-saturated toluene solution. However, CdSe-generated singlet oxygen is rather low, i.e. 5% versus 43% reported for classical photosensitisers. But the photo bleaching of classical photosensitisers is rapid compared with that of quantum dots. Nevertheless, the prolonged and repetitive exposure of quantum dot-treated cells to irradiation may have the

potential to mediate a high steady-state level of singlet oxygen, enough perhaps to induce apoptotic and/or necrotic cell death in the target tissue.^[21]

CERAMIC-BASED NANOPARTICLES AS CARRIERS FOR CANCER THERAPY

Ceramic-based nanoparticles have the potential to act as delivery system for photosensitiser agents. For example, silica-based nanospheres doped with water-insoluble photosensitisers are efficiently taken up into the cytosol of tumour cells and generate singlet oxygen *in vitro*. The size of the nanosphere is important because the lifetime of $^1\text{O}_2$ in aqueous media is in the microsecond domain, during which interval it can diffuse over a radial distance of at least 100 nm. Silica-based nanospheres are highly stable and are unlikely to release any embedded substances, although their porous matrix is permeable to triplet as well as singlet oxygen and subsequent light irradiation results in significant cell death. Experiments using silica-based nanospheres in tumour-model animals are in progress.^[22]

BIODEGRADABLE POLYMER BASED NANOPARTICLES FOR CANCER

Other approaches involve the incorporation/encapsulation of hydrophobic photosensitisers into sub-200 nm nanoparticles composed of biodegradable polymers, and polyacrylamide, or photosensitiser-stabilised gold Nanoparticles. The photocytotoxicity of the polymeric nanoparticles has been evaluated on mouse mammary tumour cells *in vitro*, rat glioma tumour cells *in vitro*, as well as on an *in vivo* chick embryo model showing inhibition of tumour cell growth more effectively than free photosensitisers and selective destruction of chick embryo vasculature of the chorioallantoic membrane while protecting surrounding tissues. In addition, the biodegradable nanoparticles show an increased residence time in blood vessels that could diminish the doses of photosensitiser agents and might be useful to overcome the post-treatment accumulation of the free drug in the skin and the eye which may last for at least one month, and the adverse effects seen during photodynamic treatment of choroidal neovascularisation associated with age-related macular degeneration, one of the leading causes of blindness in elderly people in Western countries. Furthermore, sterilisation of the polymeric nanoparticles by membrane filtration is feasible offering great advantages because many photosensitising agents may be denatured by heat or gamma sterilisation.^[923]

NANOPLATFORMS BASED ON NANOCOMPOSITE PARTICLES

A magnetic core of $\gamma\text{-Fe}_2\text{O}_3$ can be embedded within silica-based nanospheres functionalised with a targeting agent. Applying a DC magnetic field results in a selective magnetocytolysis of targeted cells only. DC magnetic fields can be generated by medical magnetic resonance imaging devices and require less power compared to devices generating AC magnetic fields used for thermotherapy. Experiments involving the synthesis of functionalised magnetic nanoparticles as carriers of photosensitisers to develop a nanoplatform with “dual lethality” combining the photocytotoxicity effect of the photosensitiser with the magnetocytolytic property are also in progress.^[24]

Recently, the synthesis of magnetic nanoparticles ($\gamma\text{-Fe}_2\text{O}_3$) and CdSe based quantum dots encapsulated in a silica shell has been reported. These materials have potential in combining targeting, bioimaging, biolabelling, and biosensing applications enabling novel platforms that are aimed at deployment for clinical applications in cancer research.^[25]

CHEMOTHERAPY

NANO-STRUCTURED POLYMER CAPSULES

Nano-structured polymer capsules could be used to deliver chemotherapy directly to tumours, leaving adjacent tissue intact. The concept of the capsule is basically a templating core, which contains drug particles, surrounded by multilayered polymer spheres with embedded light-absorbing gold nanoparticles. A lipid bilayer and tumour-specific antibodies form an outer layer. When injected into the bloodstream, the nano-structured capsules will concentrate inside tumours. When a sufficient number of capsules have gathered in malignant cells, a low energy pulse from a near-infrared laser is applied. A 10-nanosecond laser pulse is brief enough to heat the gold nanoparticles which swell up to 50 nm in diameter. The pulse is too short to damage the contents of the nano-structured capsules, but will melt the gold, rupture the polymer spheres and the nano-structured capsules will subsequently release their contents.^[26]

In clinical use the laser could be targeted through the skin, or be beamed inside the body via an endoscope. The infrared energy (100 mJ/cm^2) needed for the rupture of the nanostructured capsules is well within safety limits. The next refinement will be the down-sizing of the capsules from around $1 \text{ }\mu\text{m}$ to a couple of hundred nanometres by using

smaller drug particles. Clinical use and even animal tests are not yet within reach. However, photoactivating the capsules without damaging surrounding tissue is particularly interesting therapeutically.[²⁷].

DENDRIMER

Therapeutic agents can be attached to or embedded in a dendrimer to direct the delivery. A more advanced concept of drug delivery has been explored independently by three research teams. Chemical signal, the dendrimer skeleton falls apart in a chain reaction of several steps, releasing the constituent molecules. Released drugs, e.g. paclitaxel, kill cancerous cells whereas the degradation products of the dendrimer skeleton are not cytotoxic. A possible risk is if the trigger is activated at the wrong time or place, in which case the result could be dangerous.[²⁸].

NANOCELLS

The fundamental challenges in cancer chemotherapy are its toxicity to healthy cells and drug resistance by cancer cells. In cancer therapy anti-angiogenesis therapy is an elegant concept based on the starvation of tumour cell by impairment of blood supply. However, lack of oxygen prompt tumour cells to release a cell signaling molecule known as hypoxia-inducible factor-1 α , which triggers metastasis and the development of resistance to further chemotherapy. An obvious solution would be combining chemotherapy and antiangiogenesis.

Recently, a multifunctional nanoparticle has been designed enabling this combination. The dual-chamber, double-acting, drug-packing “nanocell” proved effective and safe, with prolonged survival, against two distinct forms of cancers, i.e. melanoma and Lewis lung cancer, in mice. Using two different widely studied biocompatible polymers, a balloon within a balloon was created, resembling an actual cell. The outer membrane of the nanocell, made of pegylated-phospholipid block-copolymer, was loaded with the anti-angiogenic drug combrestatin. The inner balloon, composed of the biodegradable and nonbioactive poly-lactic-co-glycolic acid, was loaded with the chemotherapy agent doxorubicin. Pegylation of the outer membrane creates a “stealth” surface chemistry that allows the nanocells to evade the immune system. The size of the nanocells allows tumour cells to take them up preferentially compared to other healthy cells. Once the nanocell is inside the tumour, its outer membrane disintegrates, rapidly deploying the anti-angiogenic drug. The blood vessels feeding the tumour then collapse, trapping the loaded nanoparticle in the tumour,

where it slowly releases the chemotherapeutic agent. In an in vivo mouse model the double-loaded nanocell demonstrates tumour inhibition, stops angiogenesis and avoids systemic toxicity much better than other treatment and delivery variations. Moreover, the nanocell works better against melanoma than lung cancer, indicating the need to systematically evaluate drug combinations and loading mechanisms for different cancers.[²⁹].

NANOCHIPS

Nanochips may even be used to assist in repairing damaged tissue, detecting mutated genes, or detecting high hormone levels indicative of certain malignancies. Nanochips may be capable of triggering immediate responses to inflamed, ischemic, or neoplastic tissues and simultaneously provide therapy to these tissues. Surprisingly, a silicon-based nanochannel has already been used to deliver antitumor compounds locally to unresectable tumors with zero-order kinetics. This implantable device circumvented the inconvenience of frequent local injections using novel nanotechnology applications.[³³]

RADIOTHERAPY

DENDRIMERS FOR BORON NEUTRON CAPTURE THERAPY

Dendrimers can be used in boron neutron capture therapy, which is an experimental approach to cancer treatment using a two-step process. First, a patient is injected with a non-radioactive pharmaceutical which selectively migrates to cancer cells. This component contains a stable isotope of boron (¹⁰B). Next, the patient is irradiated by a neutron beam of low-energy or thermal neutrons. The neutrons in the beam interact with the boron in the tumour causing the boron atom to split into an alpha particle and a lithium-7 ion. Both of these particles have a very short range and destroy tumour cells in which it is contained. In order to sustain a lethal reaction a large number of boron atoms must be delivered to each cancer cell requiring selective delivery.

PAMAM dendrimers containing folic acid conjugates of boronated poly (ethylene glycol) units have been prepared to target folate receptors abundantly expressed in a variety of human tumour. These in vitro studies showed receptor-dependent uptake of the dendrimer conjugates.[³⁰].

CARBON NANOTUBES FOR BORON NEUTRON CAPTURE THERAPY

Recently, water-soluble single walled carbon nanotubes (SWCNTs) with appended C2B9 units have been shown to

be Promising nanovehicles for boron delivery to tumour cells in vitro. Tumour tissue shows enhanced accumulation and retention of these modified SWCNTs. The actual mechanism of accumulation has not yet been determined.^[31].

GOLD NANOPARTICLES

Intravenous injection of gold nanoparticles (~2 nm in diameter) can enhance radiotherapy (Xrays) and results in eradication of subcutaneous mammary tumours in mice. One-year survival is 86% versus 20% with X-rays alone. Apparently, gold nanoparticles are non-toxic to mice and are cleared from the body through the kidneys.^[32].

NANOPARTICLES BASED PRODUCTS CURRENTLY AVAILABLE IN MARKET

The development of nanoparticles based products may play an important role in adding a new armamentarium of therapeutics to the pipelines of pharmaceutical companies. Currently several liposome and Nanocrystal based formulation are available in market are listed in Table 1.^[33]

Figure 1

Table 1 Several Nanoparticles based products currently available in market

PRODUCT	COMPANY	DRUG	FORMULATION	ROUTE OF ADMINISTRATION	APPLICATION
Doxil	Sequus Pharmaceuticals	Doxorubicin	Liposome	IV injection	Kaposi sarcoma in AIDS
Ambisome	NeXtar Pharmaceuticals	Amphotericin B	Liposome	IV infusion	Serious fungal and HIV infection
DauvoXome	NeXtar Pharmaceutical (Boulder, Colorado)	Daunorubicin citrate	Liposome	IV	Kaposi sarcoma in AIDS
Emend	Merck Elan (USA)	Aprepitant, MK069	Nanocrystal particles	Oral	For chemotherapy patient to delay nausea and vomiting
Abraxane	American Biosciences	Paclitaxel	Albumin bound nanoparticles	IV injection	Metastatic breast cancer
Megace ES	PAR Pharmaceuticals	Megestrol acetate	Nanocrystal particles	Oral	Treatment of a weight loss in patient with a diagnosis AIDS

FUTURE DIRECTIONS FOR NANOPARTICLES DRUG DELIVERY IN CANCER THERAPY

Future efforts in cancer therapy are envisaged to be driven by multi-functionality and modularity, i.e. creating functional modalities that can be assembled into nanoplateforms and can be modified to meet the particular demands of a given clinical situation. These nanoplateforms are independently coupled to targeting, and imaging/monitoring modalities, and can deliver selectively therapeutics intracellularly for growth suppression. Targeting modalities can be based on the recognition properties of cell-surface receptor ligands, monoclonal antibodies, nanobodies, or aptamers. Nanobodies are the smallest fragments of naturally occurring heavy-chain antibodies that have evolved to be fully functional in the absence of a light chain and have shown effective targeting

in adenocarcinoma tumour-bearing mice and have attracted attention as nanoparticles crossing the blood-brain barrier. Aptamers are DNA or RNA oligonucleotides that fold by intramolecular interaction into unique three dimensional conformations capable of binding to target antigens with high affinity and specificity. Aptamers are quickly emerging as a new powerful class of ligands that rival with antibodies in their potential for diagnostic and therapeutic application. Recently, nanoparticle aptamer bioconjugates have been developed and demonstrated proof-of-concept for targeted delivery in prostate cancer cells. The imaging/monitoring modalities can be based on traditional fluorophores, or quantum dots and superparamagnetic iron oxide nanoparticles. These constructed nanoplateforms would localise to target cells and could deliver their therapeutic payload with great precision where they are likely to be most effective, that is within the cell or even within specific organelles. Not only anticancer drugs, but also physically triggered chemical substances, such as photosensitisers, superparamagnetic iron oxide nanoparticles, or isotopes, can be applied as therapeutic agent.^[23435].

Currently, NanoCure™ Corporation (Ann Arbor, Michigan, USA) is developing dendrimer based nanoplateforms capable of delivering therapeutics (drugs and genes) to specific targeted cells coupled with imaging/monitoring modality. The initial target applications for this technology are cancers of the neck, breast and prostate. The proof-of-principle for treatment of cancer tumours of the neck has been demonstrated in animal models. Availability for clinical investigations is anticipated within three years.

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