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Review Article

TARGETING THE TARGET USING NANOPARTICLES - A REVIEW

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ABSTRACT

The challenge of drug delivery is the liberation of drug agents at the right time in a safe and reproducible manner, usually to a specific target site. Conventional dosage forms, such as orally administered pills and subcutaneous or intravenous injection, are the predominant routes for drug administration. However, pills and injections offer limited control over the rate of drug release into the body; usually, they are involved in an immediate release of the drug. This article is about how nanoparticles can be used as an effective drug delivery system to target the drug to a specific location or organ.

Keywords: Nanoparticles, Targeted drug delivery, Nanomedicine, Cancer therapeutics, Carrier systems.

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INTRODUCTION

Nanotechnology refers to the interactions of cellular and molecular components and engineered materials-typically, clusters of atoms, molecules, and molecular fragments into incredibly small particles-between 1 and 100 nm. The concept of nanoscale devices has led to the development of biodegradable self-assembled nanoparticles (NPs), which are being engineered for the targeted delivery of anticancer drugs and imaging contrast agents [4]. Nanotechnology has changed our daily lives in many ways, including in matters related to energy, the environment, and medicine. With respect to medicine, nanomaterials offer new tools to explore diseases using imaging and diagnostic applications, one and more popularly, they act as vehicles for delivering drugs or therapeutic agents to achieve better and safer treatment outcomes [6].

Consequently, to achieve therapeutic levels that extend over time, the initial concentration of the drug in the body must be high, causing peaks (often adjusted to the stay just below known levels of toxicity for the drug) that gradually diminish over time to an ineffective level. In this mode of delivery, the duration of the therapeutic effect is dependent on the frequency of dose administration and the half-life of the drug [8].

NPs used as drug delivery vehicles are generally <100 nm in at least one dimension, and consist of different biodegradable materials such as natural or synthetic polymers, lipids, or metals. NPs are taken up by cells more efficiently than larger micromolecules and therefore, could be used as effective transport and delivery systems. For therapeutic applications, drugs can be integrated into the matrix of the particle or attached to the particle surface. A drug targeting system should be in a position to control the fate of a drug entering the biological environment [3].

APPLICATIONS OF NPS IN BIOLOGY AND MEDICINE

A list of some of the applications of nanomaterials to biology or medicine are in fluorescent biological labels, drug and gene delivery, biodetection of pathogens, detection of proteins, probing of DNA structure, tissue engineering, tumor destruction through heating (hyperthermia), separation and purification of biological molecules and cells, magnetic resonance imaging (MRI) contrast enhancement and phagokinetic studies [3].

DESIGN OF NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

These drug-loaded NPs formulations that release higher doses of the drug for a prolonged period completely inhibited the proliferation of vascular smooth muscle cells [3].

Colloidal drug delivery modalities such as liposomes, micelles, or NPs have been intensively investigated for their use in cancer therapy. The effectiveness of drug delivery systems can be ascribed to their small size, reduced drug toxicity, controlled time release of the drug and modification of drug pharmacokinetics and biological distribution [3]. The primary goals for research on nanobiotechnologies in drug delivery include more specific drug targeting and delivery, reduction in toxicity while maintaining therapeutic effects, greater safety and biocompatibility, and faster development of new safe medicines [18].

The main issues in the search for appropriate carriers as drug delivery systems pertain to the following topics that are basic prerequisites for the design of novel materials. They comprise knowledge of (i) drug incorporation and release, (ii) formulation stability and shelf life, (iii) biocompatibility, (iv) biodistribution and targeting, and (v) functionality. In addition, when used solely as a carrier the possible adverse effects of residual material after the drug delivery should be considered as well. In this respect of biodegradable NPs with a limited life span as long as therapeutically needed would be optimal [18].

Parallel to the development of particulate delivery systems, the field of micro-/nano-electromechanical device-based drug delivery has also made significant headway over the past decade. In particular, implantable microchips containing nanosized reservoirs have been developed to deliver drugs for long-time periods in a precisely controlled manner; microneedles are being tested in painless transdermal drug delivery; and the incorporation of nanofeatures (e.g. nanopores, nanochannels, and NPs) in microfabricated systems are perfecting drug delivery and immunoisolation techniques [10].

NP-BASED THERAPEUTICS IN PRECLINICAL DEVELOPMENT

Besides liposomes and polymeric conjugates, the most common NP platforms today include polymeric NPs, micelles, nanoshells, dendrimers, engineered viral NPs, albumin-based NPs, polysaccharide-based NPs, metallic NPs, and ceramic NPs. These NPs have shown

therapeutic potential for almost every branch of medicine such as oncology, cardiology, immunology, neurology, endocrinology, ophthalmology, pulmonary, orthopedics, and dentistry.

Recently, biodegradable polymeric micelles with a size of 10-200 nm have attracted a lot of attention as drug delivery necessaries and have shown remarkable therapeutic potential. Polymeric micelles are formed by self-assembly of block copolymers consisting of two or more polymer chains with different hydrophobicity [1].

These copolymers spontaneously assemble into a core-shell micelle structure in an aqueous environment to minimize the system's free energy. Specifically, hydrophobic blocks form the core to minimize their exposure to aqueous surroundings whereas the hydrophilic blocks form the corona-like shell to stabilize the core through direct contact with water. This micelle structure provides an ideal drug delivery necessarily [1]. Dendrimers are members of a versatile, fourth new class of polymer architecture (i.e. dendritic polymers after traditional linear, cross linked, and branched types). Typically, daydreamers are used as well-defined scaffolding or noncontentious to conjugate, complex or encapsulate therapeutic drugs or imaging moieties. As a delivery vector, the dendritic conjugate linker or spacer chemistry plays a crucial part in determining optimum drug delivery to disease sites in conserving active drug efficacy while influencing appropriate release patterns [10].

Therapeutic antiparticle platforms in preclinical development:

a. Liposome,
b. Polymer-drug conjugate,
c. Polymeric antiparticle,
d. Dendrite, and
e. Iron oxide antiparticle [11].

NP-BASED CARRIER SYSTEMS

When designing a drug delivery system with a selective target activated release mechanism, one should consider the drug administration route, and the path of the drug(s) to the target cells, with respect to the physicochemical and biological conditions (e.g., pH, ionic strength, enzymes present, and serum albumin entrapment) and the barriers encountered (e.g., blood vessel endothelium such as blood-brain barrier, cell membrane, nuclear membrane, and nuclear pores). In the case of extracellular release, the drug delivery system is designed to liberate the drug(s) under the extracellular environment conditions in the target tumor or its microenvironment, and the drug has to be able to penetrate the cell membrane either passively by diffusion, or actively by specific transporters, or through receptor mediated endocytosis [21].

POLYELECTROLYTE CAPSULES AS UNIVERSAL CARRIER SYSTEMS

Polyelectrolyte multilayer (PEM) capsules are fabricated following a bottom-up approach through layer-by-layer (LbL) self-assembly of differently charged polyelectrolytes on top of a template particle. Hereby, the onion-shaped LbL geometry is held together predominantly by electrostatic force. Subsequent dissolution of the template particle leads to PEM capsules.

PEM capsules have several distinct features: (i) They can carry cargo in their cavity, and other functionalities can be incorporated into their PEM walls. Cargo can constitute macromolecules, hydrophobic drugs, micelles, or NPs. (ii) The cargo inside the capsule cavity is protected within the polyelectrolyte walls and does not take part in the control over pharmacokinetics and biodistribution. Cells which have incorporated capsules are also protected from direct contact with the containing cargo. (iii) Size and charge of the PEM capsules can be readily tuned. Size and charge are important parameters which affect interaction with cells. (iv) The PEM wall can be biodegradable or nondegradable, and its porosity can be tuned by the number of polyelectrolyte layers and by the PEM materials [1].

MAGNETIC NPS (MNPS) FOR TARGETED LOCAL UPTAKE AND RELEASE

The idea of exploiting magnetic guidance, which uses an implanted permanent magnet or an externally applied field, to increase the accumulation of drugs at diseased sites goes back to the late 1970s. Objects possessing a magnetic moment experience a force in magnetic field gradients. In this way, it is possible to direct and accumulates those objects at a designated target site. This concept has been successfully used, for example, for *in vivo* targeting of drug-loaded MNPs to tumor tissue [1]. As many MNPs can be loaded with each capsule, the resulting magnetic moment is rather high. Thus, even gradients generated by magnets from a toy store are large enough to trap capsules at desired positions of cell cultures in a model flow channel system. The magnetic field gradient itself does not stimulate internalization of the capsules, but it accumulates capsules by locally trapping them [1].

As many MNPs can be loaded with each capsule, the resulting magnetic moment is rather high. Thus, even gradients generated by magnets from a toy store are ample to trap capsules at desired positions of cell cultures in a model flow channel system. The magnetic field gradient itself does not inspire internalization of the capsules, but it accumulates capsules by locally trapping them [1].

The development of drug delivery systems with selectivity to pathologic sites is an ambitious goal. The principles of magnetic guidance of MNP-conjugated drugs have been applied experimentally, and have reached clinical trials as a cancer therapy. Following intravenous delivery of MNPs, an external magnetic field is utilized to concentrate MNPs at a specific target site; this procedure has been well tolerated in cancer patients [13].

FLUORESCENT NPS FOR BARCODING OF CAPSULES ENABLING SPATIALLY RESOLVED SENSING

Sensing of ions is important to a large variation of cell biological applications. One common detection technique is fluorescence detection of analyte-sensitive fluorophores. Such analyte-sensitive fluorophores are (often organic) fluorescence dyes, of which (in general) the fluorescence emission intensity selectively depends on the presence of a specific type of ion, such as H^+, K^+, Na^+, Ca_2^+, and Cl^-.

To sense ions, they must be in a position to traverse the capsule walls and reach the ion-sensitive fluorophores in the capsule cavity. As the wall of PEM capsules is porous, this is generally no problem. Porosity depends for instance on the used polyelectrolyte materials and the number of polyelectrolyte layers [1].

CARBON NANOTUBES (CNTS) IN BIOLOGY AND MEDICINE: *IN VITRO* AND *IN VIVO* DETECTION, IMAGING, AND DRUG DELIVERY

CNTs exhibit many unique intrinsic physical and chemical properties and have been intensively explored for biological and biomedical applications in the past few years. Ultrasensitive detection of biological species with CNTs can be realized after surface passivation to inhibit the non-specific binding of biomolecules on the hydrophobic nanotube surface. Electrical nanoseconds based on nanotubes provide a label-free approach to biological detection. Surface-enhanced Raman spectroscopy of CNTs opens up a method of protein microarray with detection sensitivity down to 1 fmol/L. *In vitro* and *in vivo* toxicity studies reveal that highly water soluble and serum stable nanotubes are biocompatible, nontoxic, and potentially useful for biomedical applications. *In vivo* biodistributions vary with the functionalization and possibly also the size of nanotubes, with a tendency to accumulate in the reticuloendothelial system (RES), including the liver and spleen, after intravenous administration. If well fictionalized, nanotubes may be excreted mainly through the biliary pathway in feces. Carbon nanotube-based drug delivery has shown promise in various *in vitro* and *in vivo* experiments including delivery of small interfering RNA

(siRNA), paclitaxel, and doxorubicin. Moreover, single-walled CNTs with various interesting intrinsic optical properties have been used as a novel photoluminescence, Raman, and photographic contrast agents for imaging of cells and animals. Further multidisciplinary explorations in this field may bring new opportunities in the realm of biomedicine [5]. Carbon nanohorns (CNHs) are the spherical aggregates of CNTs with an irregular horn like shape. Research studies suggest that CNTs and CNHs as potential carriers for drug delivery systems [20].

SOLID LIPID NPS (SLN) FOR PARENTERAL DRUG DELIVERY

SLN

SLN is particles made from solid lipids (i.e. lipids compacted at room temperature and also at body temperature) and stabilized by surfactant(s). By definition, lipids can be highly purified triglycerides, complex glyceride mixtures, or even waxes. Recently, SLN based on para-acyl-calix have been developed and studied. Through the work of various research groups, the carrier system SLN has been characterized intensively [14].

Nanostructured lipid carriers (NLC)

NLC have been put in place at the end of the 1990s to overcome the potential difficulties of SLN. The goal was the development of a nonparticulate lipid carrier with a certain nanostructure to increase the payload and prevent drug expulsion. This could be achieved in three ways. In the first model, spatially different lipids, for example, glycerides composed of unusual fatty acids are mixed. Using spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus to more room for the accommodation of guest molecules. The highest drug load could be obtained by mixing solid lipids with small amounts of liquid lipids (oils). This model is called "imperfect type NLC" [14].

Lipid drug conjugate (LDC)

SLN is beneficial for the incorporation of lipophilic drugs. Due to partition effects during the production process, only highly potent hydrophilic drugs which are effective in low concentrations (e.g., luteinizing hormone-releasing hormone or erythropoietin) can be firmly incorporated in the solid lipid matrix. To overcome this limitation, the so-called LDC NPs with drug loading capacities of up to 33% have been developed at the turn of the millennium. Here, an insoluble drug-lipid conjugate bulk is prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to esters or ethers). In the salt formation process, the unbound drug base and fatty acid are dissolved in a suitable solvent. The solvent is then consequently evaporated under reduced pressure. For the covalent linking, the drug (salt) and a fatty alcohol reaction in the presence of a catalyst and the LDC bulk are then purified by recrystallization. The obtained LDC bulk is then processed with an aqueous surfactant solution to an antiparticle formulation using high-pressure homogenization [14].

BIODEGRADABLE POLYMERIC NPS AS DRUG DELIVERY DEVICES

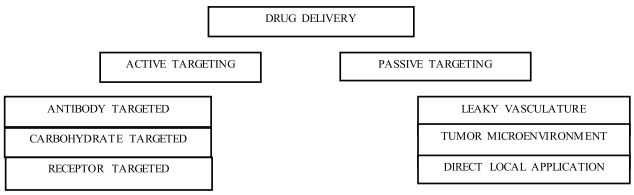
Over the past few decades, there has been considerable interest in developing biodegradable NPs as effective drug delivery devices. Various polymers have been used in drug delivery research as they can effectively deliver the drug to a target site and thus increase the salutary benefit while minimizing side effects. The controlled release of pharmacologically active agents to the precise site of action at the therapeutically optimal rate and dose regimen has been a major goal in designing such devices. Liposomes have served as potential drug carriers instead of conventional dosage forms because of their unique advantages which include the ability to protect drugs from degradation, target the drug to the site of action and reduce the toxicity or side effects [15].

Drug release from NPs and subsequent biodegradation is important for developing the successful formulations. The release rates of NPs depend on: (i) Desorption of the surface-bound/adsorbed drug, (ii) diffusion through the NP matrix, (iii) diffusion (in case of nanocapsules) through the polymer wall, (iv) NP matrix erosion; and (v) a combined erosion/diffusion process. Thus, diffusion and biodegradation govern the process of drug release [15].

NANOTECHNOLOGY IN CANCER THERAPEUTICS: DRUG DELIVERY

Nanobiotechnology is playing an important role in advances in oncology, and currently, nanotechnology is the most important chapter of nanomedicine. Nanobiotechnologies have renewed molecular diagnostics and enabled early detection of tumors and discovery of biomarkers of cancer. Various NPs are the basis of diagnostic assays for cancer as well as contrast materials for MRI. Nanobiotechnology is facilitating the discovery and development of drugs for cancer. Several nanobiotechnologies, mostly based on NPs, have been described to facilitate drug delivery in cancer, which is important for optimizing the effect of drugs and reducing toxic side effects. NPs for targeted drug delivery in cancer enable the combination of diagnostics and therapeutics and act as adjuncts to hyperthermia and photodynamic therapy [9]. The surface chemistry of the gold NPs plays an immense role in formulating an efficient drug delivery platform. Surface modification of the gold NPs not only provides an increased circulation time and thus slows down the RES uptake, when modified with polyethylene glycol molecules, but also can be easily targeted to the diseased site when coupled with specific biomolecules [21].

Mechanism of antiparticle drug delivery through two main mechanisms-passive and active targeting [4].



TARGETED KILLING OF CANCER CELLS *IN VIVO* AND *IN VITRO* WITH EPIDERMAL GROWTH FACTOR (EGF)-DIRECTED CNT-BASED DRUG DELIVERY

Carbon nanotube-based drug delivery holds great promise for cancer therapy. Herein, we report the first targeted, *in vivo* killing of cancer cells using a drug-single wall carbon nanotube (SWNT) proconsulate, and demonstrate efficacy superior to non-targeted proconsulates. First-line anti-cancer agent circulating and EGF were attached to SWNTs to specifically target squamous cancer. Moreover, non-targeted control was SWNT-cisplatin without EGF. Initially, *in vitro* imaging studies with head and neck squamous carcinoma cells (HNSCC) over expressing EGF receptors (EGFR) using Qdot luminescence and confocal microscopy showed that SWNT-Qdot-EGF proconsulates internalized rapidly into the cancer cells. Limited uptake occurred in control cells without EGF, and uptake was blocked by siRNA knockdown of EGFR in cancer cells, revealing the importance of EGFEGFR binding. Three colors, two-photon intravital video imaging *in vivo* showed that SWNT-Qdot-EGF injected into live mice was selectively taken up by HNSCC tumors, but SWNT-Qdot controls with no EGF were cleared from the tumor region in <20 minutes. HNSCC cells treated with SWNT-cisplatin-EGF were shot dead selectively, while control systems that did not feature EGF-EGFR binding did not influence cell proliferation. Most significantly, regression of tumor growth was rapid in mice treated with targeted SWNT-cisplatin-EGF relative to non-targeted SWNT-cisplatin [12].

OUTLOOK AND FUTURE CHALLENGES

Turning the potential of antiparticle systems into clinically useful formulations requires setting up clear, realistic goals. The challenges in targeted drug delivery using NPs can be overcome through understanding the limitations of antiparticle approaches and maximizing the existing capabilities of antiparticle formulations [2].

EXPLOIT THE 5% REACHING THE TARGET TUMOR

NPs go to target tumors simply as a result of blood circulation. Thus, the percentage of the administered drug reaching the tumor is similar regardless of the formulation type. The antiparticle remains around the tumor longer, because they do not diffuse back into the blood stream as easily as dissolved drug molecules. This leads to more accumulation of the drug near the tumor site. Assuming 5% of the total administered NPs can end up at the tumor site. One can make an antiparticle system a clinically useful formulation. Currently, the drug loading in most NPs is not high, usually around 10%. If the drug loading can be increased by a factor 5, it is the equivalent of delivering 25% of the total administered NPs with 10% drug loading. For example, instead of loading a drug into liposomes or polymer micelles, one can use the drug nanocrystals themselves, which deliver 100% of the drug. The surface of the nanocrystals may have to be modified by polymers or proteins for enhancement of their affinity to cells or their stability [2].

ENTERING THE TUMOR CELLS

For a drug to take effect, it needs to enter the tumor cells. Thus, improving the cellular interaction, leading to cellular uptake, is another crucial innovation. In an attempt to maximize interactions with the cell, a new nanotube approach was developed. The high affinity of NPs to the cell surface may have the added benefit of increasing the international distribution of the NPs. Extracurricular transport and, thus, tumor-targeting efficiency of NPs depends on the nature of targeting ligands attached to the antiparticle surface. Receptor-mediated phagocytosis can facilitate extravascular transport of NPs, leading to enhanced antiparticle delivery to solid tumors. It overcomes the barrier to the efficient dispersion of NPs in tumor interstitial. Efficient delivery of NPs into the tumor interstitial exposes tumor cells to lethal doses and makes them less susceptible to the development of resistance [2].

Targeting drugs to solid tumors which are localized in a particular tissue involves numerous complications, however, the issues of targeting become more and more complicated when the tumor cells start disseminating to other tissues. Understanding the molecular factors affecting metastasis is critical to identify appropriate future targets which can be utilized for targeting drugs to the tumor cells. Molecular targets would further depend on the site of metastasis of the cancer cells. Skeletal metastasis is a frequent complication of solid tumors, including breast and prostate cancer, and is usually incurable. Currently, available treatment modalities are primarily palliative and have only a transient beneficial effect. Although many new therapeutic targets have been proposed, the lack of appropriate drug delivery systems has hampered any developments in clinical options available to patients. Thus, there is a key need for a drug delivery approach which can overcome the anatomical and physiological barriers and can deliver drugs specifically at the bone metastatic site. This would not only prevent non-specific systemic adverse effects of the drugs but also allow reaching therapeutic drug concentrations at the disease site [7].

TOXICOLOGICAL HAZARDS OF NPS

General concepts

To utilize the potential of nanotechnology in nanomedicine, full attention is needed to safety and toxicological issues. For pharmaceuticals specific drug delivery formulations may be utilized to increase the so-called therapeutic ratio or index being the margin between the dose needed for clinical efficacy and the dose inducing adverse side effects (toxicity). However, also for these exclusive formulations, a toxicological evaluation is needed. This is particularly true for applications of NPs for drug delivery. In these applications of particles are brought intentionally into the human body and environment, and some of these new applications are envisaged an important improvement of health care. Opinions began to divert when toxicologists claimed that new science, methods and protocols are needed. However, the need for this is now underlined by numerous expert reports and more importantly by the following concepts:

1. Antimalarial is developed for their unique (surface) properties in comparison to bulk materials. Since the surface is the contact layer with the body tissue and a crucial determinant of particle response, these unique properties need to be investigated from a toxicological standpoint
2. NPs are attributed to qualitatively different physicochemical characteristics from micron-sized particles, which may result in changed body distribution, passage of the blood brain barrier, and triggering of blood coagulation pathways [18]
3. Effects of combustion derived NPs in environ - mentally exposed populations mainly occur in diseased individuals. Typical pre-clinical screening is almost always done in healthy animals and volunteers and risks of particles may, therefore, be detected at a very late stage [18]
4. It is an ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation [19].

CONCLUSION

Long circulation of drugs in the body is the main in successful drug delivery and drug targeting to the site of action. Targeted drug delivery to tumors can increase the selectivity for killing cancer cells, decrease the peripheral/systemic toxicity and can permit a dose escalation. Advances in the identification of tumor specific targets and development of different drug delivery approaches for tumor targeting have raised hopes for the development of a successful targeted drug delivery modality for cancer therapy. It appears that nanodrug delivery systems hold great potential to bridge some of the barriers to efficient targeting of cells and molecules in inflammation and cancer. There also is an exciting possibility to overcome problems of drug resistance in target cells and to facilitate the movement of drugs across barriers such as those in the brain. However, so far, the scientific paradigm for the possible (adverse) reactivity of NPs is lacking and we have little understanding of the basics of the interaction of NPs with living cells, organs and organisms. A conceptual understanding of biological responses to nanomaterials is needed to develop and apply safe nanomaterials in drug delivery in the future.

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