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Target Nanoparticles: An Appealing Drug Delivery Platform

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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. Nanoparticles are solid colloidal matrix-like particles made of polymers or lipids. Generally administered by the intravenous route like liposome's, they have been developed for the targeted delivery of therapeutic or imaging agents. Nanomaterials have emerged as a promising strategy in delivering therapeutic molecules effectively to diseased sites. Furthermore, most nonmaterial surfaces can be decorated with targeting ligands, enhancing their ability to home to diseased tissues through multivalent interactions with tissue-specific receptors. Thus, targeted therapy provides a means to circumvent the toxicities and lack of treatment response of conventional systemic chemotherapy. Targeted liposome's, micelles, carbon nanotubes and dendrimers incorporated with therapeutic molecules have displayed impressive anticancer effects in animal studies, and these nanomaterials are considered to be close to clinical translation due to their biocompatibility. These carriers are designed in such a way that they are independent in the environments and selective at the pharmacological site. In addition, these nanomaterials have the capability to reverse multidrug resistance a major problem in chemotherapy. Finally, tumor-homing nanosystems that amplify tumor homing can also improve the delivery of compounds to tumors, providing imaging and therapeutic options that were previously unavailable.

Keywords: Nanoparticle; Targeting; Cancer therapy; Active targeting; Passive targeting; Tumor; Nanotube; Nanoshell; Nanorods

Introduction

Recent years have witnessed unprecedented growth of research and applications in the area of nanoscience and nanotechnology. There is increasing optimism that nanotechnology, as applied to medicine, will bring significant advances in the diagnosis and treatment of disease.

Nanotechnology is enabling technology that deals with nano-meter sized objects. It is expected that nanotechnology will be developed at several levels: materials, devices and systems. The nanomaterials level is the most advanced at present, both in scientific knowledge and in commercial applications. A decade ago, nanoparticles were studied because of their size-dependent physical and chemical properties [1].

Nanospheres and nanocapsules that can be either amorphous or crystalline are the most widely used nanoparticles. They are specially designed to adsorb or encapsulate a drug, thereby protecting it against chemical and enzymatic degradation. The drug is confined in a cavity lined by a polymer membrane in nanocapsules while, there is a matrix system wherein the drug is physically and uniformly dispersed in nanospheres. In recent years, biodegradable polymeric nanoparticles have attracted the attention of numerous researchers around the world in the controlled release of drugs due to its inherent capacity in targeting particular organs/tissues and also as carriers of DNA in gene therapy and in their unique ability to deliver proteins, peptides and genes by the oral route. Nanoparticles are used for parenteral, oral, ocular and transdermal applications as well as used in cosmetics and hair care technologies, sustained release formulations and as a carrier for radio nucleotides in nuclear medicines [2].

Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates), or solid lipids. In the body, the drug loaded in nanoparticles is usually released from the matrix by diffusion, swelling, erosion, or degradation.

A nanodrug delivery system consists of a core, a particle or emulsion prepared by chemical methods to function as a carrier. Functional groups are added to the core. Such groups may include therapeutic molecules and ligands for targeting specific locations. Nanotechnology in drug delivery is exemplified by nanocrystals, liposomes, nanoparticle-protein conjugates, magnetic nanoparticles, nanogels and biodegradable nanoparticles. Table 1 represents some of the types of chemical structures and possibilities for the preparation of nanoscale materials used as pharmaceutical carrier system (reviewed in Borm and Mullers-Schulte 2006) [3]. The use of materials on the nanoscale level provides unprecedented freedom to modify some of the most fundamental properties of therapeutic carriers. Using nanoparticles, it may be possible to achieve (a) 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 into faster absorption by human body (b) targeted delivery of drugs in a cell- or tissue-specific manner; (c) transcytosis of drugs across tight epithelial and endothelial barriers; (d) delivery of large macromolecule drugs to intracellular sites of action; (e) co-delivery of two or more drugs or therapeutic modality for combination therapy; (f) visualization of sites of drug delivery by combining therapeutic agents with imaging modalities; and (g) real-time read on the in vivo efficacy of a therapeutic agent [4-6].

Nanoparticle Platforms for Biomedicine Applications

Nanomaterials have attracted much attention in the areas of biomedical and bioengineering due to a number of beneficial factors including a large surface area to volume ratio, and the possibility of ubiquitous tissue accessibility. Nanomaterials are beginning to

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allow scientist, engineers and physicians to work at the cellular and molecular level to produce major advances in the life sciences and healthcare [7]. Advances in Nanomaterials have significantly impacted the field of therapeutics delivery significantly. This is evidenced by the increase in the number of nanoparticle-based therapeutic products in development over the last two decades. A global survey conducted by the European Science and Technology Observatory (ESTO) revealed that more than 150 companies are developing nanoscale therapeutics, and 24 nanoparticle therapeutics are currently in clinical use [8]. Currently several liposome and nanocrystal based formulation are available in market are listed in Table 2 [9].

Commercial Exploration

Some of the companies that are involved in the development and commercialisation of nanomaterials in biological and medical applications are listed below (Table 3). The majority of the companies are small recent spinouts of various research institutions. Although not exhausting, this is a representative selection reflecting current industrial trends. Most of the companies are developing pharmaceutical applications, mainly for drug delivery. Several companies exploit quantum size effects in semiconductor nanocrystals for tagging biomolecules, or use bio-conjugated gold nanoparticles for labelling various cellular parts. A number of companies are applying nano-ceramic materials to tissue engineering and orthopedics'.

Current Challenges in Drug Delivery

For the majority of pharmaceuticals currently in use, the activity against certain diseases or disease sites is not based on their ability to accumulate selectively in the pathological organ, tissue or cell. Usually, the pharmaceutical agent is rather evenly distributed within the body. Moreover, to reach the site of action, the drug has to cross many biological barriers, such as other organs, cells and intracellular compartments, where it can be inactivated or express undesirable influence on organs and tissues that are involved in the pathological process. As a result, to achieve a required therapeutic concentration of a drug in a certain body compartment, one has to administer the drug in large quantities, the great part of which is just wasted in normal tissues. In addition, under these circumstances, cytotoxic and/or antigenic drugs can become the cause of many negative side effects.

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. Under such conditions, the local concentration of the drug at the disease site(s) should be high, while its concentration in other non-target organs and tissues should be below certain minimal level to prevent any negative side-reactions. Drug targeting can achieve a goal of this challenge [10,11].

Particle class	Materials	Application
Natural materials or derivatives	Chitosan Dextrane Gelatine Alginates Liposomes Starch	Drug/Gene delivery
Dendrimers	Branched polymers	Drug delivery
Fullerenes	Carbon based carriers	Photodynamics Drug delivery
Polymer carriers	Polylactic acid Poly(cyano)acrylates Polyethyleinemine Block copolymers Polycaprolactone	Drug/gene delivery
Ferrofluids	SPIONS USPIONS	Imaging (MRI)
Quantum dots	Cd/Zn-selenides	Imaging In vitro diagnostics
Various	Silica-nanoparticles Mixtures of above	Gene delivery

Table 1: Overview of nanoparticles and their applications in life sciences.

Approaches to Drug Targeting

One strategy to further improve the therapeutic index of nanoparticles therapeutics is to functionalize nanoparticles with targeting ligands. The targeting of nanoparticulate formulations focuses on both the development of new diagnostic tools and improving the efficacies of therapeutic agents. The addition of targeting ligands allows the delivery of drug-encapsulated nanoparticles to uniquely identified sites while having minimal undesired effects elsewhere. There are many different approaches to targeted drug delivery, which are classified broadly into three categories. (i) Physical or mechanical approach which requires formulation of the drug using a particulate delivery device, for eg. Magnet which by virtue of its physical localization will allow differential release of the drug [12]. (ii) Biological approach which involve delivery of the drug using a carrier system like antibodies, lecithin [13]. (iii) Chemical approach which incorporates chemical delivery systems, allow targeting of active biological molecules to specific target sites or organs, based on enzymatic activation. The following advantages of drug targeting are evident: (a) drug administration protocols may be simplified; (b) drug quantity required to achieve a therapeutic effect may be greatly reduced as well as the cost of therapy; (c) drug concentration in the required sites can be sharply increased without negative effects on non-target compartments [14].

The aim of nanoparticles entrapment of drugs are either enhanced delivery to, or uptake by, target cells and/or a reduction in the toxicity of the free drugs to non-target organs. For these aims, creation of long-lived and target specific nanoparticles are needed. Our goal is to design nanoparticle encapsulating multifunctional combinatoric drugs, and functionalize their surfaces with recognition elements that can target specific diseased cells [15,16]. Targeting approaches can be broadly classified into two areas; passive and active targeting.

Passive targeting

Passive targeting (Figure 1a) refers to the accumulation of drug or drug-carrier system at a particular site due to physico-chemical or pharmacological factors [17,18]. Solid tumors present much more favorable conditions for preferential accumulation of macromolecular drugs and colloidal sized drug delivery systems like polymeric-drug conjugates, micellar systems, polymeric nanoparticles, as well as liposome's. The increased vascular permeability coupled with the impaired lymphatic drainage in rapidly growing tumors allows an enhanced permeability and retention (EPR) effect of the nanosystems in the tumor [19,20]. However, passive targeting with nanoparticles encounters many obstacles on the way to their target; these include mucosal barriers, non-specific uptake of the particles and non-specific delivery of the drug [21]. Therefore, appropriate size and functionalization with antibodies can provide means of enhanced delivery of drugs and reduced non-specific toxicity. In addition, the drug must remain encapsulated and must not diffuse out of the particle until the particle binds to the target. It was shown that polymeric nanoparticles administered per orally could be selectively targeted to the inflamed colonic mucosa in inflammatory bowel disease [22]. Similarly, the blood brain barrier can also be crossed to access the target sites for brain delivery in some inflammatory conditions [23].

Active targeting

Active targeting employs specific modification of drug/drug-carrier nanosystems with active agents having selective affinity for recognizing and interacting with a specific cell, tissue or organ in the body. Coupling of drug carrier nanosystems to ligands allows import of thousands of drug molecules by means of receptor targeted ligands.

Product	Company	Drug	Formulation	Route of administration	Application
Doxil	Sequus Pharmaceuticals	Doxorubicin	Liposome	IV injection	Kaposi sarcoma in AIDS
Ambisome	NeXstar Pharmaceuticals	Amphotericin B	Liposome	IV infusion	Serious fungal and HIV infection
Dauno Xone	NeXstar Pharmaceuticals (Boulder, Colorado)	Daunorubicin citrate	Liposome	IV injection	Kaposi sarcoma in AIDS
Emend	Merck/Elan (USA)	Aprepitant, MK869	Nanocrystal particles	Oral	For chemotherapy patient to delay nausea and vomiting
Abraxane	American Biosciences	Paclitaxel	Albumin bound nanoparticle	IV injection	Metastatic breast cancer
Megaace ES	PAR Pharmaceuticals	Megaestrol acetate	Nanocrystal particles	Oral	Treatment of weight loss in patient with AIDS

Table 2: Nanoparticles based products currently available in market.

Company	Major area of activity	Technology
Advectus Life Sciences Inc.	Drug delivery	Polymeric nanoparticles engineered to carry anti-tumour drug across the blood-brain barrier
Alnis Biosciences, Inc.	Bio-pharmaceutical	Biodegradable polymeric nanoparticles for drug delivery
Argonide	Membrane filtration	Nanoporous ceramic materials for endotoxin filtration, orthopaedic and dental implants, DNA and protein separation
BASF	Toothpaste	Hydroxyapatite nanoparticles seems to improve dental surface
Biophan Technologies, Inc.	MRI shielding	Nanomagnetic/carbon composite materials to shield medical devices from RF fields
Capsulution NanoScience AG	Pharmaceutical coatings to improve solubility of drugs	Layer-by-layer poly-electrolyte coatings, 8–50 nm
Dynal Biotech		Magnetic beads
Eiffel Technologies	Drug delivery	Reducing size of the drug particles to 50–100 nm
EnviroSystems, Inc.	Surface desinfectant	Nanoemulsions
Evident Technologies	Luminescent biomarkers	Semiconductor quantum dots with amine or carboxyl groups on the surface, emission from 350 to 2500 nm
Immunicon	Tarcking and separation of different cell types	magnetic core surrounded by a polymeric layer coated with antibodies for capturing cells
KES Science and Technology, Inc.	AiroCide filters	Nano-TiO2 to destroy airborne pathogens
NanoBio Cortporation	Pharmaceutical	Antimicrobal nano-emulsions
NanoCarrier Co., Ltd	Drug delivery	Micellar nanoparticles for encapsulation of drugs, proteins, DNA
NanoPharm AG	Drug delivery	Polybutilcyanoacrylate nanoparticles are coated with drugs and then with surfactant, can go across the blood-brain barrier
Nanoplex Technologies, Inc		Nanobarcodes for bioanalysis
Nanoprobes, Inc.	Gold nanoparticles for biological markers	Gold nanoparticles bio-conjugates for TEM and/or fluorescent microscopy
Nanoshpere, Inc.	Gold biomarkers	DNA barcode attached to each nanoprobe for identification purposes, PCR is used to amplify the signal; also catalytic silver deposition to amplify the signal using surface plasmon resonance
NanoMed Pharmaceutical, Inc.	Drug delivery	Nanoparticles for drug delivery
Oxonica Ltd	Sunscreens	Doped transparent nanoparticles to effectively absorb harmful UV and convert it into heat
PSiVida Ltd	Tissue engineering, implants, drugs and gene delivery, bio-filtration	Exploiting material properties of nanostructured porous silicone
Smith & Nephew	Acticoat bandages	Nanocrystal silver is highly toxic to pathogenes
Quantum Dot	Luminescent biomarkers	Bioconjugated semiconductor quantum dots

Table 3: Examples of companies commercializing nanomaterials for bio and medical applications.

This modification is usually on the corona of the particle, introducing ligands, which facilitates the homing, binding and internalization of the formulation to the targeted cells (Figure 1b). Most research has focused on the specific targeting of cells expressing disease-associated biomarkers, as in the case of cancer. Various moieties have been examined as targeting agents, including vitamins, [24] carbohydrates, [25] aptamers, [26] peptides (e.g., Arg-Gly-Asp, allatostatin, trans-activating transcriptional activator) [27-29] and proteins (e.g., lectins, and transferrin) [30-31] However, active agents, such as ligands for the receptors and antibodies to the surface proteins have been used extensively to target specific cells, the majority of research to date has focused on antibodies.

Approaches for Targeted Nanoparticles in Cancer Therapy

As cancer grinding away the lives of a large section of the society, the importance of nanomedicine is gaining new heights. Conventional chemotherapeutic agents are distributed non-specifically in the body, where they affect both cancerous and normal cells, thereby, limiting the dose achievable within the tumor and also resulting in suboptimal treatment due to excessive toxicities. Molecularly targeted therapy has emerged as one approach to overcome the lack of specificity of conventional chemotherapeutic agents [32].

Novel nanomedical anticancer therapies with much lesser pain and side effects are becoming the ultimate anticancer solutions (Figure 2). In cancer treatment and detection, nanoparticles (NP) serve many targeted functions in chemotherapy, thermotherapy, radiotherapy, photodynamic therapy, immunotherapy and anti angiogenesis. Almost as intense an area of research as NP formulation is NP targeting.

Targeted drug delivery is attractive because it recapitulates some of the advantages of topical application of drugs: high local concentration

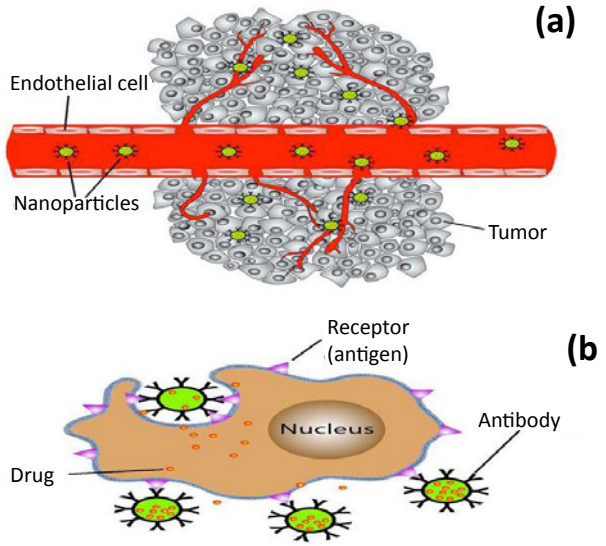

Figure 1: (a) Passive tissue targeting by nanoparticles in blood vessels. Particle directed in the target tissue as a result of leaky vessels and ineffective lymphatic drainage; (b) Active cellular targeting of nanoparticles with conjugated antibodies [21].

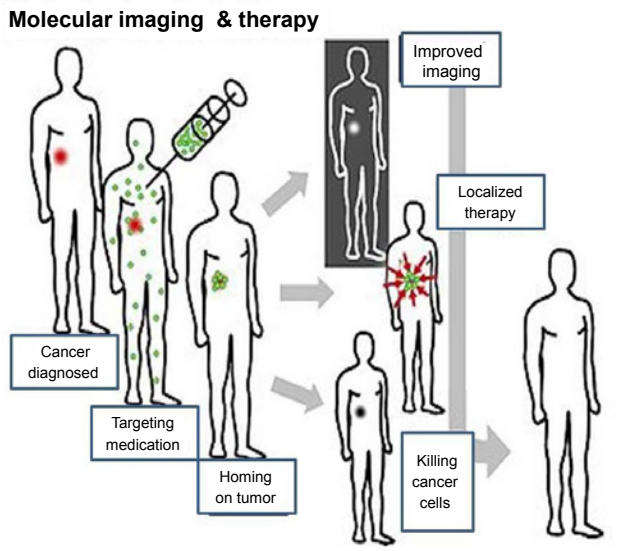

Figure 2: Nano-drug particles function in human body for cancer treatment.

and low systemic exposure. Cancer stands out as a disease most likely to benefit from targeted drug delivery. 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 [33]. 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 [34]. The targeting of nanoparticulate formulations focuses on both the development of new diagnostic tools and improving the efficacies of therapeutic agents. Tumor cells express many molecules on their surface that distinguishes them from normal cells. Traditionally, such molecules were detected with antibodies, but screening of peptide and aptamer libraries has greatly expanded number of tools available for selective binding to tumor cells [35,36].

Targeted cancer therapies that have been approved for use in specific cancers include drugs that interfere with cell growth signaling or tumor blood vessel development, promote the specific death of cancer cells, stimulate the immune system to destroy specific cancer cells, and deliver toxic drugs to cancer cells.

Because scientists call these specific molecules "molecular targets," therapies that interfere with them are sometimes called "molecularly targeted drugs," "molecularly targeted therapies," or other similar names.

The first molecular target for targeted cancer therapy was the cellular receptor for the female sex hormone estrogen, which many breast cancers require for growth. When estrogen binds to the estrogen receptor (ER) inside cells, the resulting hormone-receptor complex activates the expression of specific genes, including genes involved in cell growth and proliferation. Research has shown that interfering with estrogen's ability to stimulate the growth of breast cancer cells that have these receptors (ER-positive breast cancer cells) is an effective treatment approach. Several drugs that interfere with estrogen binding to the ER have been approved by the FDA for the treatment of ER-positive breast cancer. Drugs called selective estrogen receptor modulators (SERMs), including tamoxifen and toremifene (Fareston®), bind to the ER and prevent estrogen binding. Another drug, fulvestrant (Faslodex®), binds to the ER and promotes its destruction, thereby reducing ER levels inside cells [37].

Targeted chemotherapy using spherical gold nanoparticles

The use of gold nanoparticles attached to a molecule of a tumor-killing agent called tumor necrosis factor alpha (TNF) as well as a molecule of Thiol-derivatized polyethylene glycol (PEG-THIOL), which hides the TNF bearing nanoparticle from the immune system has been successfully examined. The PEG-THIOL allows the nanoparticle to flow through the blood stream without being attacked. The combination of a gold nanoparticle, TNF and PEG-THIOL is named Aurmine.

The nanoparticle carrying the TNF tends to accumulate in cancer tumors but does not appear to accumulate in other regions of the body, which limits the toxic effects of TNF on healthy cells. CytImmune (a nanotechnology company) uses a combination of two techniques to target the TNF-carrying nanoparticle to cancer tumors. First, the nanoparticle is designed to be too big to exit most healthy blood vessels; however some blood vessels located at the site of tumors are leaky, allowing the nanoparticle to exit the blood vessel at the tumor site. The second technique involves the TNF molecules binding to the tumor.

TNF has been shown to be most effective when administered with other chemotherapy drugs. Recently, CytImmune is planning a phase 2 trial with Aurmine combined with other chemotherapy drugs. They are also performing pre-clinical testing of another combination in which TNF, PEG-THIOL and a chemotherapy drug called paclitaxel is bound to the surface of the nanoparticle. Three other treatments are under development using nanoparticles combined with TNF and other chemotherapy drugs. It will take a while to bring these treatments through all the phases required for qualification with the FDA, however it is exciting that they have progressed from the realm of research papers to trials that will lead to targeted treatment for patients [38].

Target delivery with nanoshell in head and neck cancer

Researchers at Rice University under Prof. Jennifer West have demonstrated the use of 120 nm diameter nanoshells coated with gold to kill cancer tumors in mice. The nanoshells can be targeted to bond to cancerous cells by conjugating antibodies or peptides to the nanoshell surface. By irradiating the area of the tumor with an infrared laser, which passes through flesh without heating it, the gold is heated sufficiently to cause death to the cancer cells (Figure 3) [39]. Nanoparticles of cadmium selenide (quantum dots) glow when exposed to ultraviolet light. When injected, they seep into cancer tumors. The surgeon can see the glowing tumor, and use it as a guide for more accurate tumor removal. Auroshell™ a new discovered heat therapy to destroy cancer tumor using nanoparticles. The Auroshell™ nanoparticles circulate through a patient blood stream, exiting where the blood vessels are leaking at the site of cancer tumors. Nanoparticles are accumulating in the solid tumors. Following this accumulation, the area is illuminated with a laser that emits near-infrared light, a wavelength that has significant penetration through human tissue.

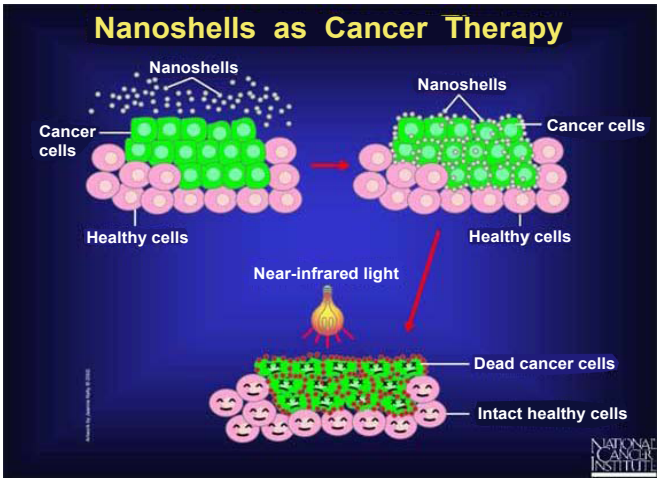

Figure 3: Nanoshells as cancer therapy.

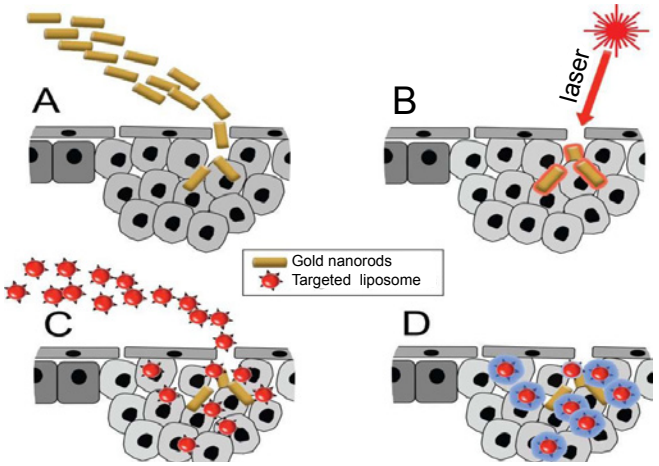

Figure 4: Treating tumors with cooperative nanoparticles. (A) Passive accumulation of gold nanorods. (B) Laser irradiation of nanorods activates tumor cells. (C) Targeted nanoparticles (liposomes) bind to tumor. (D) Activation of targeted liposomes releases drug [42].

The particles are designed to absorb this wavelength, converting the absorbed light into heat to thermally destroy the solid tumor [39].

Targeted drug delivery using carbon nanotubes

Single-walled carbon nanotubes have been highly touted for their potential as novel delivery agents for cancer detection and therapeutic agents. Now, a team of investigators from six institutions have created a multifunctional carbon nanotube that can detect and destroy an aggressive form of breast cancer.

Human epidermal growth factor receptor 2 (HER2) is one of a family of genes that help regulate the growth and proliferation of human cells. Normal cells have two copies of HER2, but about 20 to 25 percent of breast cancers consist of cells have multiple copies of the gene, resulting in the overproduction of a HER2-encoded protein that is associated with particularly fast growing and difficult to treat tumors. The team led by Huixin He, and Yan Xiao, of the National Institute of Standards and Technology (NIST) created the new dual-purpose nanostructure by attaching an anti-HER2 antibody to short carbon nanotubes. The investigators used an antibody raised in chickens. The chicken antibody reacts strongly with the target protein expressed on tumor cells while ignoring normal cells with other human proteins.

The investigators then took advantage of optical properties of carbon nanotubes to detect and then destroy HER2 breast cancer cells. Using the laser light's wavelength at 808 nanometers that will be absorbed by the nanotubes, incinerating them and anything to which they're attached-in this case, the HER2 tumor cells [40].

Nanoparticles for enhanced x-ray treatment of cancer tumors

Nanobiotix an emerging nanomedicine company is using technology that it calls 'nanoXray therapeutics' to resolve radiation therapy's biggest drawback: destruction of healthy tissue and its subsequent deleterious side effects when a high dose of x-ray is necessary. NBTXR3 is patent nanoXray therapeutics is designed to allow destruction of cancer cells only-a new treatment weapon that could be used alone, or in concert with existing anticancer protocols: chemotherapy, surgery, and immunotherapy.

The core of a NBTXR3 nanoparticle is an inactive and inert substance-not drugs-hafnium oxide that can be activated only when its electrons are excited by the application of an external beam of x-ray. Under standard external beam x-ray activation, x-rays are absorbed by NBTXR3 nanoparticles exactly as ionizing radiations are absorbed by water molecules, leading to emission of electrons losing energy and the subsequent creation of free radicals. In both cases, x-ray energy will generate electrons with kinetic energy that will be released into the medium and will generate free radicals. Because NBTXR3 is comprised of crystalline nanoparticles, it does not have deleterious effects on healthy cells, unlike chemotherapy or other systemic anticancer agents. The nanoparticles do not react directly with any biological recipient cell and tissue [41].

Targeted drug delivery using using gold nanorods and nanoparticles called liposomes

Researchers at University of California at San Diego investigate treating tumors with cooperative nanoparticles. Figure 4 illustrates a method to induce cooperative nanoparticle behavior that results in more effective delivery of treatments to tumors. This example uses a two component system consisting of gold nanorods and targeted, thermally sensitive liposomes [42]. When inject gold nanorod into blood stream, passive accumulation of gold nanorods; the gold nanorods stay in the

healthy blood vessels but exit the leaky blood vessels found at the site of tumors. The gold nanorods then accumulate in the tumor and an infrared laser is used to heat the gold nanorods, thereby heating the tumor. The gold nanorods absorb laser energy, heating the surrounding tissue. This localized rise in temperature increases tissue permeability and induces expression of receptor proteins on the surface of the tumor cells. When the drug packed liposome is injected into the bloodstream and the amino acids on the nanoparticles attach to the proteins; the heat has pushed to the surface of the tumor and more of the drug is delivered to the tumor.

In this example, thermally responsive liposomes containing a drug payload are heated with a second laser pulse, inducing rupture of the liposome shell and release of its contents.

Targeted nanoparticles for pancreatic cancer

Pancreatic cancer is characterized by a strong desmoplastic reaction and poor vascularisation. Therefore, the lack of early detection as well as inefficient drug delivery into the tumor tissue hampers successful treatment. To overcome these hurdles, multifunctional nanotechnology systems in progress to improve pancreatic cancer diagnosis and treatment response. Nano-scale delivery systems provide a bio-compatible platform allowing combined delivery of different therapeutic agents that act synergistically in one single vehicle. In addition, these systems can be multi-functionalized with targeting peptides or antibodies, which results in the selective targeting of the tumor site and the cancer (stem) cells. To address this fundamental issue in pancreatic cancer treatment, [43] proposed a targeted drug delivery platform consisting of a lipid-polymer hybrid nanoparticle (NP) to carry therapeutic payloads and a selectively reduced anti-carcinoembryonic Antigen (CEA) half-antibody (hAb) to target pancreatic cancer cells. The lipid-polymer hybrid NPs consist of a biodegradable and biocompartible hydrophobic polymeric core made of poly D,L-lactic-co-glycolic acid (PLGA), a monolayer of phospholipids, and an outer corona layer made of polyethylene glycol (PEG). Despite their complex structure, these hybrid NPs are synthesized in a simple, single-step fashion, which allows future scale-up production [44]. These target NPs can preferentially bind to pancreatic cancer cells rather than normal cells. Given the high drug loading capacity of each lipid-polymer hybrid NP, the cancer cells are expected to be destroyed even though only few NPs are taken up by one cell.

This way the drugs specifically reach the tumor tissues in the correct ratios and thus lower doses are expected to be required, which would reduce the number and severity of putative side effects.

Nanoparticle Drug Delivery Systems in Chemotherapy of Tuberculosis (TB)

Treatment of TB involves continuous, frequent multiple drug dosing. Adherence to treatment and the outcome of therapy could be improved with the introduction of long-duration drug formulations releasing the antimicrobial agents in a slow and sustained manner, which would allow reduction in frequency and dosing numbers. The achievements and challenges of drug delivery using nano-particles have been covered in numerous publications over the last few years. The effectiveness of pulmonary drug delivery using nanoparticles was demonstrated in a number of studies [45]. The pharmacokinetics and antibacterial effect of the nanoparticle bound anti-TB drugs administered via respiratory route was investigated in guinea pigs [46]. The dose was delivered via a suitable facemask connected to the compressor–nebulizer system. A single nebulization of rifampin (RMP), isoniazid (INH), and pyrazinamide (PZA) co encapsulated in PLG nanoparticles to guinea pigs resulted in sustained therapeutic drug levels in the plasma for 6 to 8 d and in the lungs for up to 11 d. This effect was similar to that obtained after oral administration of the nanoparticulate formulation of the same drugs. In nebulization of nanoparticles to *M. tuberculosis*– infected guinea pigs at every 10th day, no tubercle bacilli could be detected in the lungs after only five doses of treatment, whereas 46 daily doses of orally administered drug were required to obtain an equivalent therapeutic benefit. A sterilizing effect was also achieved when the drugs were loaded in solid lipid nanoparticles [47]. No tubercle bacilli could be detected in the lungs/spleen after seven doses of treatment of infected guinea pigs with drug-loaded solid lipid nanoparticles. It is noteworthy that the solid lipid nanoparticles display important advantages, such as the composition (physiologic compounds) and the possibility of large-scale production favored by the feasibility to avoid organic solvents in the manufacturing process [48].

Targeted Nanoparticles for Drug Delivery Through the Blood-Brain Barrier

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia among the elderly, affecting 5% of Americans over age 65, and 20% over age 80. An excess of senile plaques (beta-amyloid protein) and neurofibrillary tangles (tau protein), ventricular enlargement, and cortical atrophy characterizes it. Unfortunately, targeted drug delivery to the central nervous system (CNS), for the therapeutic advancement of neurodegenerative disorders such as Alzheimer's, is complicated by restrictive mechanisms imposed at the blood-brain barrier (BBB). Opsonization by plasma proteins in the systemic circulation is an additional impediment to cerebral drug delivery. Polymeric nanoparticles are the promising candidates to deliver drugs beyond the BBB for the scrutiny of the central nervous system [49].

The biodegradable polymeric nanoparticles (NPs) with appropriate surface modifications can deliver drugs of interest beyond the BBB for diagnostic and therapeutic applications in neurological disorders, such as AD. The physicochemical properties of the NPs at different surfactant concentrations, stabilizers, and amyloid-affinity agents could influence the transport mechanism.

Brain cancers

The delivery of therapeutic agents to the brain across the BBB is the limiting factor in the treatment of brain cancer. A very restricted number of liposoluble small molecules (MW < 400 Da) cross the BBB by free diffusion. All the other molecules must use specific systems to be transported across the BBB. Therefore, the future for treatment of malignant brain cancers relies on the development of therapies targeting the markers and transporters of the tumor-associated cerebral endothelium, at the primary tumor sites and also at the invasive areas [50].

The targeting agents may be antibodies, directed toward an antigen residing on the target tissue, and may be covalently conjugated via an appropriate chemical bond either directly to the drug or to a vector, such as a nanoparticulate device. Most of the targets identified have been related to molecules associated with enhanced angiogenesis or increased nutrient demand of the tumors. Some drugs have been incorporated into carriers bearing ligands or antibodies for recognition

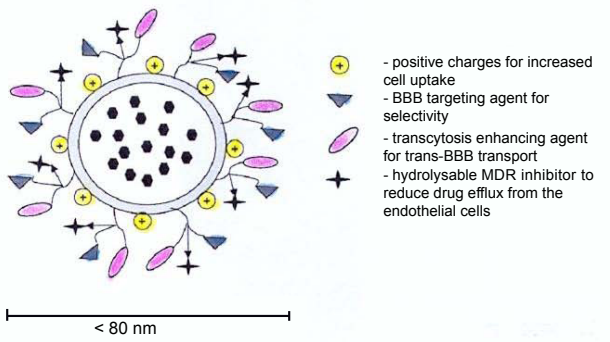

Figure 5: Structure of a model BBB drug nanoparticle delivery system. MDR means multidrug resistance.

by cell surface receptors expressed by target cells. Major obstacles include the physiological stability of these structures and their transport across biological barriers (BBB), for the delivery of therapeutic drugs. In addition, for maximal efficacy, drugs must reach their targets in the appropriate location within tumor cells, drug release from the carrier must also be achieved [51-53].

Thus, an ideal theoretical therapeutics-delivery nanoparticles system for brain cancer (Figure 5) would be one that: (i) selectively targets diseased BBB; (ii) bears an inhibitor of the efflux pump linked by a locally hydrolysable bond, and (iii) transports drugs across the cerebral vasculature and delivers them to their target, that is, the brain cancer cells. Only nanoparticulate systems can offer this diversity.

In order to be efficient and selective, nanocarriers able to ferry anti-cancer agents across the BBB to treat primary and secondary sites of aggressive brain cancers, must be very complex entities. The optimal nanocarrier will contain the anti-cancer agent in the core of a polymeric sheet, whose surface has been decorated with a BBB targeting and transport-enhancing molecule, and has enough positive charges to enhance uptake by brain tumor vasculature and inhibitor(s) for drug resistance mechanisms at the BBB and the tumor cells.

Tumor Targeting and Imaging by Magnetic Iron Oxide Nanoworms

Park et al. [54] discovered that nanostructure with an elongated assembly of iron oxide (IO) cores (referred as nanoworms), NWs) would improve the ability of nanoparticles to circulate, target, and image tumors. They found that the geometry of the nanoparticles (elongated versus spherical) influences their efficacy both in vitro and in vivo by enhancing their magnetic relaxivity in magnetic resonance imaging (MRI), increasing their ability to attach to tumor cells in vitro owing to enhanced multivalent interactions between peptide-modified NW and cell receptors, and amplifying their passive accumulation in vivo.

Targeted Delivery of Chemoradiation

Advances in nanotechnology have let to developing a targeted NP platform that is capable of delivering both chemotherapy and radiotherapy. Such an NP may improve efficacy and lower toxicity of chemoradiotherapy.

The first multifunctional NP platform intended for the codelivery of chemotherapeutics and therapeutic radioisotopes (ChemoRad NP). Previous studies have incorporated radioisotopes into NPs for biodistribution and pharmacokinetics, none of these studies have utilized the NPs for the delivery of chemoradiation [55]. The main challenge for engineering a ChemoRad NP lies in incorporating therapeutic doses of radioisotopes into NPs without affecting NP characteristics, including size, surface charge, stability and drug delivery profile. Potential compartments for radioisotope incorporation include the NP surface, the NP core, or a combination of the two.

The following design criteria were used in the engineering of the ChemoRad NP: [56]

- The NP platform is comprised of natural or biocompatible and biodegradable/bioeliminable materials to facilitate potential clinical translation;
- The NPs should have minimal release of radioisotopes prior to reaching the tumor to minimize potential toxicity;
- The NPs should have size range of 50–100 nm, which has been shown to be optimal for tumor accumulation/targeting.

Based on these criteria, Wang et al. [57] developed the ChemoRad NP using a biodegradable poly (D,L-lactic-co-glycolic acid) (PLGA) polymer and biocompatible lipids using docetaxel, indium^{111} and yttrium^{90} as model drugs. The ChemoRad NP can encapsulate chemotherapeutics (up to 9% of NP weight) and radiotherapeutics (100 mCi of radioisotope per gram of NP) efficiently and deliver both effectively. Using prostate cancer as a disease model, the research group demonstrated the targeted delivery of ChemoRad NPs and systematically examined the structural morphology, size, stability, drug release profile and radioisotope chelation properties of the ChemoRad NP, followed by evaluating its targeting ability and therapeutic effectiveness.

Conclusion

The development of targeted nanoparticles as therapeutic agents has generated great enthusiasm in both academia and industry. Targeted nanoparticles have shown exciting results in preclinical studies, demonstrating their potential as therapeutics carriers. However, several challenges remain in their development. The addition of targeting ligands increases targeted delivery but also compromises the 'stealth' surface of nanoparticles. Therefore, targeted nanoparticles should be engineered and formulated with precise control of the targeting ligand density on their surfaces. In the coming years, many more targeted nanoparticles including targeted polymeric nanoparticles will be entering clinical trials. These nanoparticles will probably have higher intracellular uptake, higher target tissue concentration, improved efficacy and lower toxicity compared with non-targeted nanoparticles, making them the 'ultimate' delivery vehicles for therapeutic agents. By perfecting the nanoparticle surface and size, as well as the targeting ligand, more and better targeted nanoparticle systems will be discovered. One day, we may finally formulate a therapeutic carrier that can truly treat target tissue without affecting normal cells.

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