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NANOTECHNOLOGY ASSISTED DRUG DELIVERY SYSTEM FOR IMPROVED CANCER TREATMENT

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ABSTRACT

In medicine, the use of nanoparticles as drug delivery systems for cancer treatment can improve the overall pharmacological properties of commonly used drugs in chemotherapy. nanoparticles as drug delivery systems solve a number of issues associated with conventional therapeutic agents, including their poor water solubility (at least, for most anticancer drugs), lack of targeting capability, nonspecific distribution, systemic toxicity, and low therapeutic index The clinical success, as well as the ease with which surface modifications can be made to both liposome and micelles to accommodate targeting ligands have made these nanocarriers in particular attractive candidates for future work involving targeted drug delivery. Compared to direct drug delivery, delivery through a carrier can increase the efficacy of a drug, but decrease the side effects by utilizing the enhanced permeability and retention (epr) effect and tumor-specific targeting although not targeted, there are clinically approved liposomal-based drugs that are currently used to treat various types of cancers. Furthermore, there are several other formulations involving both of these nanocarriers, which are now in various stages of clinical trials.

Key words: Drug Delivery, Cancer Chemotherapy, Nanoparticles, Polymer- And Liposome-Systems

INTRODUCTION

Nanoscale devices are 100 to 10,000 times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body. Nanodevices are suitable to serve as customized, targeted drug delivery vehicles to carry large doses of chemotherapeutic agents' or therapeutic genes into malignant cells while sparing healthy cells. Nanodevices can be constructed by the molding or etching, top-down approach, or by assembling, structures atom-by-atom or molecule by molecule, bottom-up approach.

Cancer is a group of diseases, which involves uncontrollable and abnormal growth by means of the potential to invade or spread to other parts of the body. Due to lack of target specificity and advocating high toxic adverse effect, chemotherapy is less opted for cancer treatment. Nanotechnology has greatly revolutionized the therapy of cancer. It minimizes the current limitations in conventional therapy. Thus, nanoparticles increase the target specificity and therapeutic utility of drug **[2].** Passive and ligand based targeting mechanism, nanoparticles directly target to the tumor site for treatment. Nanomedicines include polymeric nanoparticles, dendrimers, polymer molecules, polymersomes, polyplexes, and polymer–drug/protein conjugates. This will result in the improvement of cancer therapeutics. The broad scope for chemically modifying polymer has versatility in delivering system. In the field of the scientific research, nanotechnology mainly including the magnetic, materials development and biomedicine, optics, information technology. Nanomedicine has a wide application provides fundamental benefits in nanotechnology **[1,3].**

Chemotherapy

Chemotherapy (also called chemo) is a type of treatment that uses drugs to destroy cancer cells. Chemotherapy works by stopping or slowing the growth of cancer cells, which grow and divide quickly. but it can also harm healthy cells that divide quickly, such as those that line your mouth and intestines or cause your hair to grow. Damage to healthy cells may cause side effects. Often, side effects get better or go away after chemotherapy is over.

Chemotherapy may be given in many ways. Some common ways include:

- **Oral** the chemotherapy comes in pills, capsules, or liquids that you swallow
- **Intravenous** (iv)the chemotherapy goes directly into a vein
- **Injection** the chemotherapy is given by a shot in a muscle in your arm, thigh, or hip, or right under the skin in the fatty part of your arm, leg, or belly.
- **Intrathecal** the chemotherapy is injected into the space between the layers of tissue that cover the brain and spinal cord.
- **Intraperitoneal** (ip) the chemotherapy goes directly into the peritoneal cavity, which is the area in your body that contains organs such as your intestines, stomach, and liver.
- **Intra-arterial (IA)**The chemotherapy is injected directly into the artery that leads to the cancer.
- **Topical** The chemotherapy comes in a cream that you rub onto your skin.

Chemotherapy is often given through a thin needle that is placed in a vein on your hand or lower arm. Your nurse will put the needle in at the start of each treatment and remove it when treatment is over. IV chemotherapy may also be given through catheters or ports, sometimes with the help of a pump.

- **Catheter**

  A catheter is a thin, soft tube. A doctor or nurse places one end of the catheter in a large vein, often in your chest area. The other end of the catheter stays outside your body. Most catheters stay in place until you have finished your chemotherapy treatments. Catheters can also be used to give you other drugs and to draw blood. Be sure to watch for signs of infection around your catheter. See the section about infection for more information.

- **Port**

  A port is a small, round disc that is placed under your skin during minor surgery. A surgeon puts it in place before you begin your course of treatment, and it remains there until you have finished. A catheter connects the port to a large vein, most often in your chest. Your nurse can insert a needle into your port to give you chemotherapy or draw blood. This needle can be left in place for chemotherapy treatments that are given for longer than one day. Be sure to watch for signs of infection around your port. See the section about infection for more information.

- **Pump**

  Pumps are often attached to catheters or ports. They control how much and how fast chemotherapy goes into a catheter or port, allowing you to receive your chemotherapy outside of the hospital. Pumps can be internal or external. External pumps remain outside your body. Internal pumps are placed under your skin during surgery **[4].**

Scope of nanoparticles

Metastatic melanoma is a highly aggressive malignancy that has traditionally been very difficult to treat. However, after decades of basic research into the signal transduction pathways that promote cancer cell survival, chemo resistance, growth, and crosstalk with the immune system, targeted therapies have now been developed that offer-improved survival for patients with metastatic melanoma. Some of the most promising therapies that have been developed include ipilimumab, an anti-cytotoxic T lymphocyte antigen 4 antibody that enhances t-cell activity in the tumor, and selective braf inhibitors, such as vemurafenib that blocks tumors cell proliferation in patients with activating braf mutations. Although these treatments offer substantial hope for patients, they are not without their drawbacks, which include adverse side-effects, drug resistance, and eventual relapse. Nanotherapeutics holds significant promise to circumvent these shortcomings and has the additional advantage of potentially functioning as a diagnostic device. We will discuss the scope of the use of such multimodal nanoparticles for melanoma treatment and ask whether such particles can offer patients with metastatic melanoma improved prognoses for the future **[5].**

The tumor cell

The malignant cell is characterized by acceleration of the cell cycle genomic alterations invasive growth increased cell mobility chemo taxis changes in the cellular surface secretion of lytic factors, etc.

Morphological and functional characteristics of the malignant cell

Morphologically, the cancerous cell is characterized by a large nucleus, having an irregular size and shape, the nucleoli are prominent, and the cytoplasm is scarce and intensely colored or, on the contrary, is pale.

The nucleus of neoplastic cells plays through its changes a main role in the assessment of tumor malignancy.

Ultra structural characteristics are related to nucleus segmentation, invaginations, changes in chromatin, such as heterochromatin reduction, increase of interchromatin and perichromatin granules, increase of nuclear membrane pores, formation of inclusions, etc.

The nucleolus is characterized by hypertrophy, macro- and micro segregation, its movement towards the membrane, numerical increase and formation of intranuclear canalicular systems between the nuclear membrane and the nucleolus.

Mitoses are characteristic of malignant cells. The number of mitoses increases, atypical mitosis forms with defects in the mitotic spindle appear, which results in triple or quadruple asters and dissymmetrical structures and atypical forms of chromosomes.

Nuclear changes explain the presence of different cell clones and genetic anomalies associated with these changes. In intensely anaplastic tumors, the presence of gigantic nuclei and multinucleate cells expresses abnormal divisions.

These morphological characteristics reflect the changes occurring at metabolic level, with the augmentation of structures in relation to cell division and the attenuation of structures associated to other metabolisms.

The cytoplasm also undergoes changes, new structures appear or normal structures disappear. The accumulation of ribosomal and messenger RNA in the cytoplasm makes it basophilic. Malignant cells have a small cytoplasmic amount, frequently with vacuoles.

The granular endoplasmic reticulum has the appearance of a simplified structure. Amorphous, granular of filamentous material can accumulate in the cisternae.

Fragmentation and degranulation are frequently found, with the interruption of connections between the granular endoplasmic reticulum and mitochondria. Fingerprint like formations are not uncommon.

The decrease of the granular endoplasmic reticulum from tumor cells occurs concomitantly with an increase of free ribosomes and polysomes, which shows an enhanced production of proteins necessary for the cell growth process.

The agranular endoplasmic reticulum is, during the initiation phase, hyper plastic, without being correlated with functional hyperactivity. In other malignancy phases, the endoplasmic reticulum undergoes a reduction.

The Golgi apparatus in malignant cells is generally poorly developed, which involves a positive correlation with the lack of tumor cell differentiation. The cells that have completely lost differentiation sporadically exhibit a Golgi apparatus.

Mitochondria decrease in volume with tumor development. Mitochondria show a high variability of shape and volume, and huge mitochondria can be sometimes observed. Abnormal glycolysis processes occur in mitochondrial membranes, known in the literature as the "Warburg phenomenon". Changes in mitochondrial crystals occur, inclusions are present in the matrix, and pyknotic images can appear. The longitudinal distribution of mitochondria involves a cytochrome oxidase insufficiency.

Peroxisomes are only present in tumors formed by cells that normally contain these organelles, such as hepatocytes. It has been established that the number of peroxisomes from malignant cells is reversely proportional to growth speed and expresses the degree of differentiation loss **[6].**

Nanoparticulate carriers as non-invasive delivery systems to brain tumors

Non-invasive delivery systems employing nanoparticulate carriers represent another valuable approach for enhancing therapeutic agents' permeability across the BBB. Recent evidence suggests that the physiologic upper limit of pore size in the BBB of malignant glioma microvasculature is approximately 12 nm. It follows that nanoparticle smaller than 12 nm with long blood half-lives would be able to cross effectively the BBB of malignant glioma microvasculature.

The use of nanosystems (colloidal carriers) mainly focuses on liposomes and polymeric nanoparticles while other systems including solid lipid nanoparticles, polymeric micelles and dendrimers are also studied.

Following intravenous administration, the colloidal systems can extravasate into brain tumor but to a less extent of normal brain tissue because of the disrupted BBB of brain tumors vessels **[7].** Which leads to a more selective drug delivery into brain tumors.

This passive targeting of nanoparticles in brain with disrupted BBB is known as "Enhanced Permeability and Retention (EPR)" effect, which plays a critical role in drug delivery to solid tumors. Particles such as liposomes, which typically range between 50 to 150 nm, would remain within the microvasculature and small chemotherapy drugs would diffuse across the liposome membrane and then across the pores with the BBB of malignant gliomas.

An important requirement for using nanocarriers *via* systemic route is their ability to circulate in the bloodstream for a prolonged period of time. However, after intravenous administration, they often interact with the reticuloendothelial system (RES), leading to a rapid removal from systemic circulation **[8].**

This process mainly depends on particle size, charge and surface properties of the nanocarrier To minimize the interactions with the RES, poly (ethylene glycol) (PEG) coating or direct chemical linking of PEG to the particle surface extends plasma residence times. However, PEGylated carriers are not easily transported across the BBB resulting to their low affinity for brain tissue. Nevertheless, the nanosystems may still be useful tools for non-invasive CNS drug delivery if they are substrates of active-tranporting systems including carrier-mediated transport, receptor-mediated endocytosis and adsorptive-endocytosis **[9].** Another advantage of this approach is that imaging agents can be encapsulated within the particle along with the anticancer drug allowing non invasive monitoring of drug delivery to brain tumors **[10]** Colloidal systems, such as liposomes and nanoparticles, have shown promising features as drug carriers to target brain tumors after intravenous administration, and this technology is currently in early preclinical development phase.

Liposomes

Liposomes have in olden times been used as carrier systems for the delivery of therapeutic agents because of their easy preparation, good biocompatibility, low toxicity and commercial availability. Conventional liposomes are rapidly cleared from circulation by macrophages of the RES, which limits their developability as drug delivery systems. Extended circulation time can be accomplished either by decreasing the particle size (<100 nm) or by liposome-surface modification with PEG (stealth liposomes).

To specifically target PEGylated liposomes to the brain, they can be additionally modified with monoclonal antibodies against glial fibrillary acidic proteins, transferrin receptors (OX-26), or human insulin receptors **[11].**

For example, to effectively deliver the anticancer drug 5-fluorouracil (5-FU), known to poorly penetrate the brain via a systemic route, into the brain, transferrin was conjugated to the surface of liposomes. Transferrin conjugated liposomes were prepared by coupling the -NH_2 groups present on the surface of stearylamine containing liposomes with the -COOH groups of transferring, and the biodistribution of free 5-FU, non-coupled and coupled liposomes bearing 5-FU were determined following a single intravenous injection in rats **[12]** An average of 10-fold increment of drug uptake in the brain was observed after the liposomal delivery of 5-FU, while the transferrin-coupled liposomes caused a 17-fold enhancement in the brain uptake of 5-FU, suggesting involvement of transferrin receptors on the BBB possibly through a receptor-mediated endocytosis process **[13].**

To achieve tumor-specific delivery of sodium borocaptate ($Na_2{}^{10}B_{12}H_{11}SH$, BSH) to malignant glioma, an application of boron neutron capture therapy (BNCT), transferrin-conjugated PEGylated liposomes have been proposed **[14].** BCNT is based on the nuclear reactions between ^{10}B and thermal neutrons to give high linear energy transfer alpha particles (^4He) and lithium-7 (^7Li) nuclei ($^{10}B + 1n \rightarrow {}^7Li + {}^4He$). The resulting lithium ions and alpha particles are high linear energy transfer particles with strong biological effects. Their small distribution in tissue (5-9 mm) reduces non-specific radiation damages. Despite that, selective delivery of a sufficient number of ^{10}B atoms to tumor cells is also important **[15].**

The ^{10}B concentrations in U87D human glioma cells from three boron delivery systems (bare BSH, PEG-BSH, and transferrin-conjugated PEGylated liposomes, TF-PEG-BSH) were determined *in vitro* and *in vivo* by using inductively coupled plasma-atomic emission spectrometry (ICP-AES) ^{10}B delivery in tumor tissue by TF-PEG-BSH was highly selective and efficient among the three systems evaluated.

Moreover, the survival rate in tumor-bearing mice after BNCT was best in the TF-PEG-BSH group, suggesting that TF-PEG-BSH is a potent Boron delivery system for BNCT due to its efficacy and selectivity **[15].**

Modified liposomes have also been used for enhancing gene delivery to brain tumors. Torchilin and coworkers investigated the potential of *trans*-activating transcriptional peptide (TATp)-modified liposomes to enhance the delivery of a gene encoding the green fluorescent protein (pEGFP-N1), to intracranial human brain tumor U-87 MG cells in nude mice. TATp-liposomes demonstrated an enhanced delivery of pEGFP-N1 *in vivo* with better selectivity compared to plasmid-loaded liposomes [16**]** Thus, TATp-liposomes is a promising delivery system for transferring genes to human brain tumors *in vivo.*

Nanoparticles

Nanoparticles (NPs) are solid colloidal particles made of polymeric materials with sizes ranging from 1-1000 nm. NP includes both nanocapsules, a core-shell structure (a reservoir system), and nanospheres (a matrix system). NPs are used as a carrier system in which the drug is dissolved, entrapped, encapsulated, adsorbed or chemically linked to the surface. In addition, NPs are advantageous because of its high drug-loading capacity and protection against chemical and enzymatic degradation. Among the biodegradable polymers, poly(lactic acid-co-glycolic acid) (PLGA) is most used being FDA approved for delivery purpose and easily processed into nanoparticles having up to size of 200 nm in diameter. Similar to liposomes, NPs are rapidly cleared from the blood following intravenous administration. To minimize interactions with the RES, NPs need to be small (<100 nm). The biodistribution of NPs have been shown to be altered, specifically, with better uptake in endothelial cells, by coating NPs with hydrophilic surfactants or by covalently linking PEG-(PEGylation) or polyethylene oxide-chains on their surface. An interesting application of NPs has been reported by Chertok *et al*., **[17]**who explored the possibility of using magnetic NPs, composed of a magnetic (e.g. iron oxide/magnetite) core and a biocompatible polymeric shell (e.g. dextran, starch), to target brain tumors. Magnetic NPs (12 mg Fe/kg) were injected in 9L-gliosarcomas bearing rats under a magnetic field. MR images were acquired prior to administration of NPs and immediately after at 1 h intervals for 4 h. Image analysis revealed that magnetic targeting induced a 5-fold increase in the total glioma over non-targeted tumors and a 3.6-fold enhancement in the target selectivity index (e.g., NPs accumulation in glioma over the normal brain).

In addition, thermotherapy using magnetic NPs (i.e., magnetic fluid hyperthermia) has been investigated [18] In this study, magnetic fluids were directly injected into tumors and subsequently heated in an alternating magnetic field, which enables precise heating of almost every part of the body. *In vivo*, it has been documented with good overall tolerability in a number of cancers including GBM **[18].**

Tsutsui and coworkers **[19]** examined the effect of bionanocapsules (BNCs) on drug delivery to brain tumors. These BNCs are composed of the surface antigen of hepatitis B virus and various components such as chemical compounds, protein, genes and small interference RNA (siRNA). To selectively target brain tumors, BNCs were conjugated with anti-human EGFR antibody that recognizes EGFRvIII known to overexpress in a variety of human malignancies of epithelial origin, particularly in gliomas. Indeed, the BNCs were both efficiently and selectively delivered to glioma cells in Gli36 glioma cell lines (expressing EGFRvIII but not wild-type EGFR) and Gli35 tumor bearing rats, indicating another promising brain tumor-targeting drug delivery system.

Schneider *et al.*, **[20]** employed polybutyl cyanoacrylate NPs for the combined delivery of a vaccine and an antisense nucleotide to brain tumors. The rationale for this combination was that activating the immune systems by an active specific immunization with Newcastle-Disease-Virus infected tumor cells and blocking the transforming-growth-factor (TGF)-β production by TGF-β antisense oligonucleotides could be beneficial for brain tumors therapy.

The polybutyl cyanoacrylate NPs in the study were coated with polysorbate 80 that facilitates the BBB penetration. It has been demonstrated that animals treated with the NPs survived longer than untreated controls with reduced TGF-β-levels and increased rates of activated CD25+ T-lymphocytes. Thus, this combined vaccination/gene therapy approach may offer a novel, “double-punch” attack to crack the immune defence of the very aggressive glioblastoma.

Solid lipid nanoparticles (SLNs) have also been reported for delivering drugs to the CNS. SLNs are dispersions of solid lipids stabilized with emulsifier or emulsifier/co-emulsifier complex in water.

Solid lipids employed to prepare SLNs include widely used food lipids and commonly used emulsifiers including poloxamers, polysorbates and bile salts. Like liposomes and NPs, the biodistribution of SLNs can be manipulated by modifying the surface physico-chemical properties of SLNs to improve specificity of tissue delivery.

In recent years, the potential use of SLNs for brain drug delivering has been widely explored, and an interesting review on this topic has been published **[21].** Specifically, brain delivery of antitumor drugs, including camptothecin, doxorubicin and paclitaxel, incorporated into SLNs and PEGylated SLNs were studied **[22].** Significantly higher drug concentrations were detected in the brain when the antitumor drugs were encapsulated and delivered in SLNs, suggesting that SLNs may be capable of overcoming the BBB. In comparison with surfactant coated polymeric NPs (specifically useful in bypassing BBB), SLNs are advantageous in several counts including low intrinsic cytotoxicity, physical stability, protection of labile drugs from degradation, controlled release, and easy preparation. Interestingly, the very low cytotoxicity of SLNs and biodegradability of lipids used in their preparation makes them very attractive candidates for brain delivery and particularly for the treatment of brain tumors **[23]**. The efficacy of SLNs as carriers of different types of antineoplastic agents (such as doxorubicin, paclitaxel and the prodrug Cholesteryl butyrate) in brain tumor therapy has been reported in an experimental rat brain glioma model. It was demonstrated that doxorubicin prepared in SLNs achieved 12- (after 30 min) to 50- (after 24 hours) folds higher intratumoural concentrations compared to free solutions. In addition, in the contralateral healthy hemisphere in which BBB was not disrupted, doxorubicin-SLNs achieved subtherapeutic concentrations, while the free drug did not reach significant levels. Furthermore, i.v. administration of paclitaxel incorporated in SLNs to normal rabbits produced drug concentrations in brain tissue ten-folds higher than paclitaxel control solutions. These results strongly suggested that SLNs are able to successfully deliver cytotoxic drugs into the brain and to induce effective anti-tumoral response.

Polymeric micelles and dendrimers

Polymeric micelles are formed spontaneously in aqueous solutions of amphiphilic block copolymers and have core-shell architecture. Self-assembly occurs when the copolymer concentration reaches a threshold value known as the critical micelle concentration (CMC).

The size of polymeric micelles usually varies from ca. 10 to 100 nm. The core is composed of hydrophobic polymer blocks [e.g., poly(propylene glycol) (PPG), poly(D,L-lactide), poly(caprolactone), etc.] and a shell of hydrophilic polymer blocks (e.g., PEG). Of particular interest are Pluronic block copolymers that contain two hydrophilic PEG and one hydrophobic PPG blocks (PEG-PPG-PEG). They were shown to cross the membranes of cultured brain microvessel endothelial cells and to inhibit P-gp**[23].**

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