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Nanotechnology in Drug Delivery System

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Abstract: ***Nanotechnology hold tremendous potential as an effective drug delivery system. In this review we discussed recent developments in nanotechnology for drug delivery. To overcome the problems of gene and drug delivery, nanotechnology has gained interest in recent years. Nanosystems with different compositions and biological properties have been extensively investigated for drug and gene delivery applications. To achieve efficient drug delivery it is important to understand the interactions of nanomaterials with the biological environment, targeting cell-surface receptors, drug release, multiple drug administration, stability of therapeutic agents and molecular mechanisms of cell signalling involved in pathobiology of the disease under consideration. Several anti-cancer drugs including paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been successfully formulated using nanomaterials. Quantom dots, chitosan, Polylactic/glycolic acid (PLGA) and PLGA-based nanoparticles have also been used for in vitro RNAi delivery. Brain cancer is one of the most difficult malignancies to detect and treat mainly because of the difficulty in getting imaging and therapeutic agents past the blood-brain barrier and into the brain. Anti-cancer drugs such as loperamide and doxorubicin bound to nanomaterials have been shown to cross the intact blood-brain barrier and released at therapeutic concentrations in the brain. The use of nanomaterials including peptide-based nanotubes to target the vascular endothelial growth factor (VEGF) receptor and cell adhesion molecules like integrins, cadherins and selectins, is a new approach to control disease progression.***

I. INTRODUCTION

Nanoparticles 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. Nanoparticles 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 either be integrated in the matrix of the particle or attached to the particle surface. A drug targeting system should be able to control the fate of a drug entering the biological environment. Nanosystems with different compositions and biological properties have been extensively investigated for drug and gene delivery applications. An effective approach for achieving efficient drug delivery would be to rationally develop nanosystems based on the understanding of their interactions with the biological environment, target cell population, target cell-surface receptors, changes in cell receptors that occur with progression of disease, mechanism and site of drug action, drug retention, multiple drug administration, molecular mechanisms, and pathobiology of the disease under consideration. It is also important to understand the barriers to drug such as stability of therapeutic agents in the living cell environment. Reduced drug efficacy could be due to instability of drug inside the cell, unavailability due to multiple targeting or chemical properties of delivering molecules, alterations in genetic makeup of cell-surface receptors, over-expression of efflux pumps, changes in signalling pathways with the progression of disease, or drug degradation. For instance, excessive DNA methylation with the progression of cancer [7] causes failure of several anti-neoplastic agents like doxorubicin and cisplatin. Better understanding of the mechanism of uptake, intracellular trafficking, retention, and protection from degradation inside a cell are required for enhancing efficacy of the encapsulated therapeutic agents.

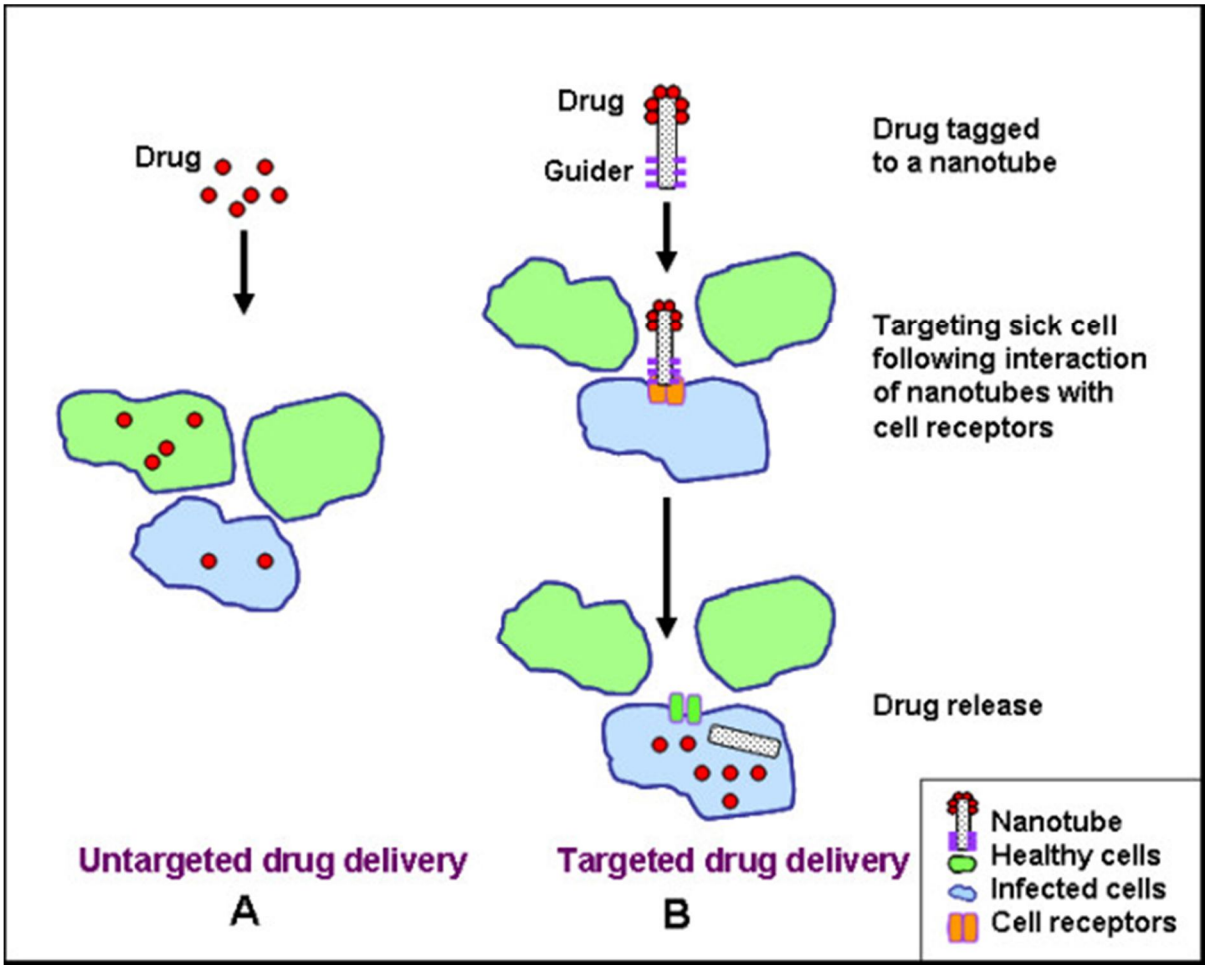
the challenges with use of large size materials in drug delivery, some of which include poor bioavailability, in vivo stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, generalized side effects, and plasma fluctuations of drugs. Of recent, several researches in nanodrug delivery have been designed to overcome these challenges through the development and fabrication of nanostructures. It has been reported that, nanostructures have the ability to protect drugs from the degradation in the gastrointestinal tract, the technology can allow target delivery of drugs to various areas of the body. The technology enables the delivery of drugs that are poorly water soluble and can provide means of bypassing the liver, thereby preventing the first pass metabolism Nanotechnology increases oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a long time, releasing the incorporated drug in a controlled fashion, leading to less plasma fluctuations and minimized side-effects.

Nanoscale size nanostructures are able to penetrate tissues and are easily taken up by cells, allowing for efficient delivery of drugs to target sites of action. Uptake of nanostructures has been reported to be 15–250 times greater than that of microparticles in the 1–10 um range. Nanotechnology improves performance and acceptability of dosage forms by increasing their effectiveness, safety, patient adherence, as well as ultimately reducing health care costs. It may also enhance the performance of drugs that are unable to pass clinical trial phases. Nanotechnology definitely promises to serve as drug delivery carrier of choice for the more challenging conventional drugs used for the treatment and management of chronic diseases such as cancer, asthma, hypertension, HIV and diabetes.

II. DESIGN OF NANOTECHNOLOGY – BASED DRUG DELIVERY SYSTEMS

Nanoparticles can be used in targeted drug delivery at the site of disease to improve the uptake of poorly soluble drugs, the targeting of drugs to a specific site, and drug bioavailability. A schematic comparison of untargeted and targeted drug delivery systems is shown in Figure 1. Several anti-cancer drugs including paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been successfully formulated using nanomaterials. Polylactic/glycolic acid (PLGA) and polylactic acid (PLA) based nanoparticles have been formulated to encapsulate dexamethasone, a glucocorticoid with an intracellular site of action. Dexamethasone is a chemotherapeutic agent that has anti-proliferative and anti-inflammatory effects. Thnds to the cytoplasmic receptors and the subsequent drug-receptor complex is transported to the nucleus resulting in the expression of certain genes that control cell proliferation. These drug-loaded nanoparticles formulations that release higher doses of drug for prolonged period of time completely inhibited proliferation of vascular smooth muscle cells.

Figure 1.



Colloidal drug delivery modalities such as liposomes, micelles or nanoparticles have been intensively investigated for their use in cancer therapy. The effectiveness of drug delivery systems can be attributed to their small size, reduced drug toxicity, controlled time release of the drug and modification of drug pharmacokinetics and biological distribution. Too often, chemotherapy fails to cure cancer because some tumor cells develop resistance to multiple anticancer drugs. In most cases, resistance develops when cancer cells begin expressing a protein, known as p-glycoprotein that is capable of pumping anticancer drugs out of a cell as quickly as they cross through the cell's outer membrane. New research shows that nanoparticles may be able to get anticancer drugs into cells without triggering the p-glycoprotein pump. The researchers studied *in vivo* efficacy of paclitaxel loaded nanoparticles in paclitaxel-resistant human colorectal tumors. Paclitaxel entrapped in emulsifying wax nanoparticles was shown to overcome drug resistance in a human colon adenocarcinoma cell line (HCT-15). The insolubility problems encountered with paclitaxel can be overcome by conjugating this drug with albumin. Paclitaxel bound to bio-compatible proteins like albumin (Abraxane) is an injectable nano-suspension approved for the treatment of breast cancer. The solvent Cremophor-EL used in previous formulations of paclitaxel causes acute hypersensitivity reactions. To reduce the risk of allergic reactions when receiving paclitaxel, patients must undergo pre-medication using steroids and anti-histamines and be given the drug using slow infusions lasting a few hours. Binding paclitaxel to albumin resulted in delivery of higher dose of drug in short period of time. Because it is solvent-free, solvent-related toxicities are also eliminated. In Phase III clinical trial, the response rate of Abraxane was about twice than that of the solvent-containing drug Taxol.

III. NANOPARTICLE-MEDIATED DELIVERY OF SIRNA

Short interfering RNA (siRNA) is emerging as a robust method of controlling gene expression with a large number of applications. Translation of nucleic acid-based therapy to clinical studies will require significant advances in the delivery system. Quantum dots (QD) have been used to monitor RNAi delivery. PLGA and PLA based nanoparticles have also been used for *in vitro* RNAi delivery. Although there has been some success in the delivery of siRNA using various nanomaterials, tracking their delivery and monitoring their transfection efficiency is difficult without a suitable tracking agent or marker. Designing an efficient and self-tracking transfection agent for RNA interference is a big challenge. Recently, Tan *et al* synthesized chitosan nanoparticles encapsulated with quantum dots and used such nanomaterial to deliver human epidermal growth factor receptor-2 (HER2/neu) siRNA. Such a novel nano carrier helped in monitoring the siRNA by the presence of fluorescent QDs in the chitosan nanoparticles. Targeted delivery of HER2 siRNA to HER2-overexpressing SKBR3 breast cancer cells has been specific with chitosan/quantum dot nanoparticles surface labeled with HER2 antibody targeting the HER2 receptors on SKBR3 cells.

Labeling of nanoparticles with a fluorescent marker, such as Cy-5, helps in visualizing uptake and accumulation of nanotubes using a fluorescent microscope. Recently, Howard *et al* used such nanoparticles conjugated with siRNA specific to the BCR/ABL-1 junction sequence and found 90% reduced expression of BCR/ABL-1 leukemia fusion protein in K562 (Ph(+)) cells. Effective *in vivo* RNA interference was also achieved in bronchiolar epithelial cells of transgenic EGFP mice after nasal administration of chitosan/siRNA formulations. These findings highlight the potential application of this novel chitosan-based system in RNA-mediated therapy of systemic and mucosal disease.

IV. CANCER

A. Targeting Cancer Cells with Nanoparticles

Cancer is one of the most challenging diseases today, and brain cancer is one of the most difficult malignancies to detect and treat mainly because of the difficulty in getting imaging and therapeutic agents across the blood-brain barrier and into the brain. Many investigators have found that nanoparticles hold promise for ferrying such agents into the brain. Apolipoprotein E was suggested to mediate drug transport across the blood-brain barrier. Loperamide, which does not cross the blood-brain barrier but exerts antinociceptive effects after direct injection into the brain, was loaded into human serum albumin nanoparticles and linked to apolipoprotein E. Mice treated intravenously with this complex induced antinociceptive effects in the tail-flick test. The efficacy of this drug delivery system of course depends upon the recognition of lipoprotein receptors. Kopelman and colleagues designed Probes Encapsulated by Biologically Localized Embedding (PEBBLE) to carry a variety of unique agents on their surface and to perform multiple functions. One target molecule immobilized on the surface could guide the PEBBLE to a tumor. Another agent could be used to help visualize the target using magnetic resonance imaging, while a third agent attached to the PEBBLE could deliver a destructive dose of drug or toxin to nearby cancer cells. All three functions can be combined in a single tiny polymer sphere to make a potent weapon against cancer. Another anti-cancer drug, doxorubicin, bound to polysorbate-coated nanoparticles is able to cross the intact blood-brain barrier and be released at therapeutic concentrations in the brain.

Smart superparamagnetic iron oxide particle conjugates can be used to target and locate brain tumors earlier and more accurately than reported methods. It is known that folic acid combined with polyethylene glycol can further enhance the targeting and intracellular uptake of the nanoparticles. Therefore, nanomaterial holds tremendous potential as a carrier for drugs to target cancer cells.

B. Targeting Angiogenesis with Nanoparticles

Robust angiogenesis underlies aggressive growth of tumors. Therefore, one of the mechanisms to inhibit angiogenesis is to starve tumor cells. Angiogenesis is regulated through a complex set of mediators and recent evidence shows that integrin αvβ3 and vascular endothelial growth factors (VEGFs) play important regulator roles. Therefore, selective targeting of αvβ3 integrin and VEGFs is a novel anti-angiogenesis strategy for treating a wide variety of solid tumors. One approach is to coat nanoparticles with peptides that bind specifically to the αvβ3 integrin and the VEGF receptor. The synthetic peptide bearing Arg-Gly-Asp (RGD) sequence is known to specifically bind to the αvβ3 integrin expressed on endothelial cells in the angiogenic blood vessels, which can potentially inhibit the tumor growth and proliferation. Following hydrophobic modifications, glycol chitosan is capable of forming self-aggregated nanotube and has been used as a carrier for the RGD peptide, labeled with fluoresein isothiocyanate (FITC-GRGDS). These nanotubes loaded with FITC-GRGDS might be useful for monitoring or destroying the angiogenic tissue/blood vessels surrounding the tumor tissue. Our research group has been studying biological responses of RGDSK self-assembling rosette nanotubes (RGDSK-RNT). These rosette nanotubes are a novel class of nanotubes that are biologically inspired and naturally water soluble upon synthesis. hese nanotubes are formed from guanine-cytosine motif as building blocks. However, one of the novel properties of the RNT is the ability to accept a variety of functional groups at the G/C motif which imparts functional versatility to the nanotubes for specific medical or biological applications. Therefore, the RNTs can be potentially modified to target a variety of therapeutic molecules in vivo to treat cancer and inflammatory diseases.

V. NANOSYSTEMS IN INFLAMMATION

A. Targeting Macrophages to control Inflammation

The potential of macrophages for rapid recognition and clearance of foreign particles has provided a rational approach to macrophage-specific targeting with nanoparticles. Macrophages' ability to secrete a multitude of inflammatory mediators allows them to regulate inflammation in many diseases. Therefore, macrophages are potential pharmaceutical targets in many human and animal diseases. Although macrophages are capable of killing most of the microbes, many microorganisms (*Toxoplasma gondii*, *Leishmania sp*, *Mycobacterium tuberculosis* and *Listeria monocytogenes*) have developed potential ability to resist phagocytosis activity of macrophages. These pathogens subvert a macrophage's molecular machinery designed to kill them and come to reside in modified lysosomes. Therefore, nanoparticles-mediated delivery of antimicrobial agent(s) into pathogen-containing intracellular vacuoles in macrophages could be useful to eliminate cellular reservoirs. This system can be used to achieve therapeutic drug concentrations in the vacuoles of infected macrophages and reduction in side effects associated with the drug administration and the release of pro-inflammatory cytokines. Polyalkylcyanoacrylates (PACA) nanoparticles have been used as a carrier for targeting antileishmanial drugs into macrophages. This nanomaterial did not induce interleukin-1 release by macrophages. Therefore, similarly designed nanosytems could be very useful in targeting macrophage infections in chronic diseases.

The antifungal and anti-leishmanial agent amphotericin B (AmB) has been complexed with lipids-based nanotubes to develop a less toxic formulation of AmB. Gupta and Viyas formulated AmB in trilaurin based nanosize lipid particles (emulsomes) stabilized by soya phosphatidylcholine as a new intravenous drug delivery system for macrophage targeting. Nanocarrier-mediated delivery of macrophage toxins has proved to be a powerful approach in getting rid of unwanted macrophages in gene therapy and other clinically relevant situations such as autoimmune blood disorders, T cell-mediated autoimmune diabetes, rheumatoid arthritis, spinal cord injury, sciatic nerve injury, and restenosis after angioplasty. Alternatively, nanoparticles with macrophage-lethal properties can also be exploited. Exploiting a variety of macrophage cell receptors as therapeutic targets may prove a better strategy for antigen delivery and targeting with particulate nanocarriers.

B. Targeting Inflammatory Molecules

In the past two decades, many cell adhesion molecules have been discovered. Cell adhesion molecules are glycoproteins found on the cell surface that act as receptors for cell-to-cell and cell-to-extracellular matrix adhesion. These cell adhesion molecules are divided into four classes called integrins, cadherins, selectins, and the immunoglobulin superfamily.

These molecules are required for the efficient migration of inflammatory cells such as neutrophils and monocytes into inflamed organs and generation of host response to infections. There is, however, considerable evidence that excessive migration of neutrophils in inflamed lungs leads to exaggerated tissue damage and mortality. Therefore, a major effort is underway to fine tune the migration of neutrophils into inflamed organs. Recent advancements of the understanding of the cell adhesion molecules has impacted the design and development of drugs (i.e. peptide, proteins) for the potential treatment of cancer, heart and autoimmune diseases. These molecules have important roles in diseases such as cancer, thrombosis and autoimmune diseases such as type-1 diabetes. The RGD peptides have been used to target integrins αvβ3 and αvβ5, and peptides derived from the intercellular adhesion molecule-1 (ICAM-1) have been used to target the αvβ2 integrin. Peptides derived from αvβ2 can target ICAM-1 expressing cells. Cyclic RGD peptides have been conjugated to paclitaxel (PTX-RGD) and doxorubicin (Dox-RGD4C) for improving the specific delivery of these drugs to tumor cells. Mice bearing human breast carcinoma cells (i.e., MDA-MB-435) survived the disease when treated with Dox-RGD4C, while all the untreated control mice died because of the disease.This conjugate targets αvβ3 and αvβ5 integrins on the tumor vasculature during angiogenesis.

Extracellular regulated kinases (ERK) may regulate apoptosis and cell survival at multiple points that include increasing p53 and BAX action, increasing caspase-3 and caspase-8 activities, decreasing Akt activity, and increasing expression of TNF-α. Our research group is investigating the interaction of RGD-RNT to αvβ3 integrins, following cell signaling through P38 kinases and its function in human lung epithelial cells, and bovine and Equine neutrophil migration. Cyclo PenITDGEATDSGC peptide (cLABL peptide), derived from the I-domain of the α subunit of Leukocyte Function-Associated Factor-1 (LFA-1) is known to bind ICAM-1. cLABL peptide has been conjugated with methotrexate (MTX) to give MTX-cLABL conjugate. Because ICAM-1 is upregulated during tissue inflammation and several different cancers, this conjugate may be useful for directing drugs to inflammatory and tumor cells. The anti-inflammatory activity of MTX is due to the suppression of production of anti-inflammatory cytokines such as (interleukin-6) IL-6 and (interleukin-8) IL-8. Thus, the activity of MTX-cLABL conjugate was compared to MTX in suppressing the production of these cytokines in human coronary artery endothelial cells stimulated with TNF-α. MTX-cLABL is more selective in suppressing the production of IL-6 than IL-8, which is opposite to MTX. PLGA nanoparticles coated with cLABL peptides have also been shown to upregulate ICAM. More detailed information on the mechanism(s) of internalization and intracellular trafficking of cell adhesion molecules is required to be exploited for delivering drug molecules to a specific cell type or for diagnosis of cancer and other diseases (heart and autoimmune diseases).

C. Smart Drug Delivery Systems

Ideally, nanoparticulate drug delivery system should selectively accumulate in the required organ or tissue and at the same time, penetrate target cells to deliver the bioactive agent. It has been suggested that, organ or tissue accumulation could be achieved by the passive or antibody-mediated active targeting, while the intracellular delivery could be mediated by certain ligands or by cell-penetrating peptides. Thus, a drug delivery system (DDS) should be multifunctional and possess the ability to switch on and switch off certain functions when necessary. Another important requirement is that different properties of the multifunctional DDS are coordinated in an optimal fashion. Thus, for example, if the system is to be constructed that can provide the combination of the longevity allowing for the target accumulation and specific cell surface binding allowing, two requirements must be met; the half-life of the carrier in the circulation should be long enough and second, the internalization of the DDS by the target cells should proceed fast enough not to allow for the carrier degradation and drug loss in the interstitial space. Intracellular transport of bioactive molecules is one of the key problems in drug delivery. Nanoparticulate DDS, such as liposomes and micelles, are frequently used to increase the efficacy of drug and DNA delivery and targeting. So far, very few successful attempts have been made to deliver various drug carriers directly into the cell cytoplasm, bypassing the endocytic pathway, to protect drugs and DNA from the lysosomal degradation, thus enhancing drug efficiency and DNA incorporation into the cell genome. Within the multifunctional DDS, it has been postulated that, the development of a DDS built in such a way that during the first phase of delivery, a nonspecific cell-penetrating function is shielded by the organ/tissue-specific delivery will be possible. Upon accumulating in the target, protecting polymer or antibody attached to the surface of the DDS via the stimuli-sensitive bond should detach under the action of local pathological conditions such as abnormal pH or temperature and expose the previously hidden second function allowing for the subsequent delivery of the carrier and its cargo inside cells. While such DDS should be stable in the blood for a long time to allow for an efficient target accumulation, it has to lose the protective coat inside the target almost instantly to allow for fast internalization thereby minimizing the washing away of the released drug or DNA. Intracellular trafficking, distribution, and fate of the carrier and its cargo can be additionally controlled by its charge and composition, which can drive it to the nuclear compartment or toward other cell organelles.

It has been reported within the past few years, that certain proteins and peptides (such as TAT peptide) can enter cell cytoplasm directly and even target cell nuclei. Certain proteins and peptides have also been used for the intracellular delivery of small drug molecules, large molecules (enzymes, DNA), and nanoparticulates (quantum dots, iron oxide nanoparticles, liposomes). The mechanism of this phenomenon is currently a subject of investigation, although important progress has been made, as some reports show that electrostatic interactions and hydrogen bonding lay behind certain proteins and peptides-mediated direct transduction of small molecules, while the energy-dependent macropinocytosis is responsible for certain proteins and peptides-mediated intracellular delivery of large molecules and nanoparticulates with their subsequent enhanced release from endosomes into the cell cytoplasm.

One of the most outstanding achievements in the drug delivery field was the development of smart drug delivery systems (SDDSs), also called stimuli-sensitive delivery systems. The concept is based on rapid transitions of a physicochemical property of polymer systems upon a stimulus. This stimulus includes physical (temperature, mechanical stress, ultrasound, electricity, light), chemical (pH, ionic strength), or biological (enzymes, biomolecules) signals and such stimuli can either be internal, resulting from changes in the physiological condition of a living subject, or ‘‘external’’ signals, artificially induced to provoke desired events. SDDS provides a programmable and predictable drug release profile in response to various stimulation sources. Fig 1 below shows a typical smart drug delivery system;

D. Smart drug delivery system -- Gold nanocage covered with polymer

Depending on the desired applications, one may design different drug delivery systems for enhanced therapeutic efficiency with low systemic toxicity and side effects. SDDS has several advantages compared to conventional drug delivery systems. The conventional controlled release systems are based on the predetermined drug release rate irrespective of the environmental condition at the time of application. On the other hand, SDDS is based on the release-on-demand strategy, allowing a drug carrier to liberate a therapeutic drug only when it is required in response to a specific stimulation. The best example of SDDS has been self-regulated insulin delivery systems that can respond to changes in the environmental glucose level. One of the most widely used SDDSs has been polymeric micelles. Many polymeric micelles consisting of hydrophobic and hydrophilic polymer blocks have been developed. They have been found to dissolve water-insoluble drugs, such as doxorubicin or paclitaxel, at high concentrations. When administered to the body, drug release from polymeric micelles usually depends on simple diffusion, degradation of the micelle blocks, or disruption of the micelles by body components.

The release kinetics of the loaded drug can be modulated by varying the degradation rate of hydrophobic polymer blocks, but because the degradation rate is usually very slow, the loaded drug is released by diffusion from polymeric micelles. This slow release by passive diffusion may not be desirable, as the polymeric micelles reaching the target site need to release their contents fast. To solve this problem, smart polymeric micelles have been designed to liberate the loaded therapeutic agent at the targeted site fast. For example, Lee et al, reported that Poly (ethylene glycol)-b-polyhistidine (PEG-b-PHis) forms micelles only over the pKb of the polyhistidine block (pH 6.5–7.0). It is interesting to know that, the pKb can be adjusted by varying the molecular weight of polyhistidine. Since solid tumors have a slightly acidic environment, a small reduction in pH to less than 7 at the tumor site triggers dissociation of the polymeric micelle to release its contents. In a separate study, Lee et al reported that, PEG-b- polyhistidine micelles containing doxorubicin effectively killed multi-drug resistant MCF-7 cells at pH 6.8. Similarly, Hruby et al, reported that, SDDS can achieve a highly localized drug accumulation at target sites even though it is administered parenterally. It is therefore postulated that, SDDS with enhanced targeting property is highly promising in increasing the efficiency and efficacy of therapy while at the same time minimizing side effects.

E. Nanotechnology in imaging and diagnosis

Diagnosis of a disease is one of the most crucial steps in the healthcare process. All diagnoses are desired to be quick, accurate and specific to prevent ‘false negative’ cases. In vivo imaging is a non-invasive technique that identifies signs or symptoms within a patient's live tissues, without the need to undergo surgery. A previous improvement in diagnostic imaging techniques is the use of biological markers that can detect changes in the tissues at the cellular level. The aim of using a biological marker is to detect illnesses or symptoms, thereby serving as an early detection tool. Notably, some of these high precision molecular imaging agents have been developed through the use of nanotechnologies. In addition to diagnosis, imaging is also vital for detecting potential toxic reactions, in controlled drug release research, evaluating drug distribution within the body and closely monitoring the progress of a therapy. Potential drug toxicity can be reduced with the possibility of monitoring the distribution of drugs around the body and by releasing the drug as required.

VI. DIAGNOSTIC IMAGING

Imaging techniques such as X-ray, ultrasound, computed tomography, nuclear medicine and magnetic resonance imaging are well established, and are widely used in biochemical and medical research. However, these techniques can only examine changes on the tissue surface relatively late in disease progression, although they can be improved through the use of contrast and targeting agents based on nanotechnologies, to improve resolution and specificity, by indicating the diseased site at the tissue level. Currently used medical imaging contrast agents are primarily small molecules that exhibit fast metabolism and a non-specific distribution, and can thus potentially result in undesirable toxic side effects. This particular area is where nanotechnologies make their most significant contribution in the field of medicine, by developing more powerful contrast agents for almost all imaging techniques, as nanomaterials exhibit lower toxicity, and enhanced permeability and retention effects in tissues. The size of the nanoparticles significantly influences its biodistribution, blood circulation half-life, cellular uptake, tissue penetration and targeting. Table II summarises some examples of nanoparticles used as contrast agents in molecular imaging.

The use of nanoparticles in X-rays has some limitations. In order to enhance the contrast, a number of heavy atoms must be delivered into the target site without causing any toxic reactions. This can be achieved using stable and inert surface atoms, such as gold and silver. Hence, gold nanoshells have garnered significant attention, due to its low toxicity. Gold nanoshells are heavy metal nanoparticles (dielectric core) encapsulated in gold shells and have been proposed to be one of the most promising materials in optical imaging of cancers. Gold nanoshells are cost-effective, safe due to its non-invasive property and may provide high resolution imaging. Gold nanoshells have similar physical characteristics to gold colloids, as they both possess a unified electronic response of the metal to light resulting in active optical absorption. Gold nanoshells are widely employed by researchers as contrast agents in the Optical Coherence Tomography of cancer cells, as the optical resonance of gold nanoshells can be adjusted accurately over a wide range, including near-infrared, where tissue transmissivity is higher. Table III shows the various types of nanomaterials used as contrast agents in pre-clinical investigations and in clinical use. Significantly more research and pre-clinical studies are required to understand and predict the effects of these nanomaterials in biologics.

A. In situ diagnostic devices

In situ diagnostic devices, such as capsule endoscopy cameras, have been shown to be successful in the clinical stage. These devices can locate and image the bleeding site and other internal problems via oral ingestion. It is hypothesized that in the future, these devices will incorporate nano-scaled sensors for chemicals, virus, bacteria and pH to broaden their utility and applications.
Moreover, these devices are also being developed as an alternative safe and precise means of drug-loaded capsules in drug delivery systems.

B. Nanotechnology in Drug Delivery

Therapy typically involves delivering drugs to a specific target site. If an internal route for drug delivery is not available, external therapeutic methods, such as radiotherapy and surgical procedures are employed. These methods are often used interchangeably or in combination to combat diseases. The goal of therapy is to always selectively remove the tumours or the source of illness in a long-lasting manner. Nanotechnologies are making a compelling contribution in this area through the development of novel modes for drug delivery, and some of these methods have proven effective in a clinical setting and are clinically used. For example, doxorubicin a drug which exhibits high toxicity, can be delivered directly to tumour cells using liposomes (Doxil®) without affecting the heart or kidneys. Additionally, paclitaxel incorporated with polymeric mPEG-PLA micelles (Genexol-PM®) are used in chemotherapeutic treatment of metastatic breast cancers. The success of nanotechnologies in drug delivery can be attributed to the improved in vivo distribution, evasion of the reticuloendothelial system and the favourable pharmacokinetics.

A perfect drug delivery system encompasses two elements: Control over drug release and the targeting ability. Side effects can be reduced significantly, and drug efficiency can be ensured by specifically targeting and killing harmful or cancerous cells. Additionally, controlled drug release can also reduce the side effects of drugs. Benefits of nanoparticle drug delivery systems include minimised irritant reactions and improved penetration within the body due to their small size, allowing for intravenous and other delivery routes. The specificity of nanoparticle drug delivery systems is made possible by attaching nano-scaled radioactive antibodies that are complementary to antigens on the cancer cells with drugs, and these approaches have produced desirable results, exhibiting improved i) drug bioavailability, ii) delivery of drugs specifically to the target site, and iii) uptake of low solubility drugs. Table IV summarises the advantages of nanoparticles over conventional fine particles

C. Nanotechnology and Cancer Treatment

Staggering numbers of individuals suffer from cancer worldwide, highlighting the need for an accurate detection method and novel drug delivery system that is more specific, efficient and exhibits minimal side effects (41). Anticancer treatments are often regarded as superior if the therapeutic agent can reach the specific target site without resulting in any side effects. Chemical modifications of the surface of nanoparticle carriers may improve this required targeted delivery. One of the best examples of modifications at the surface of nanoparticles is the incorporation of PEG or polyethylene oxide. These modifications enhance not only the specificity of drug uptake, but also the tumour-targeting ability. Incorporating PEG avoids the detection of nanoparticles as foreign objects by the body's immune system, thus allowing them to circulate in the bloodstream until they reach the tumour. Additionally, the application of hydrogel in breast cancer is a prime example of this innovative technology. Herceptin is a type of monoclonal antibody used in breast cancer treatment by targeting human epidermal growth factor receptor 2 (HER2) on cancer cells. A vitamin E-based hydrogel has thus been developed that can deliver Herceptin to the target site for several weeks with just a single dose. Due to the improved retention of Herceptin within the tumour, the hydrogel-based drug delivery is more efficient than conventional subcutaneous and intravenous delivery modes, thus making it a better anti-tumour agent. Nanoparticles can be modified in several ways to prolong circulation, enhance drug localisation, increase drug efficacy and potentially decrease the development of multidrug resistance through the use of nanotechnologies.

There are several studies using FDA-approved nano drugs, such as Abraxane®, Doxil® or Genexol-PM® as adjuvants in combinatory cancer treatment. Abraxane®, a paclitaxel albumin-stabilised nanoparticle formulation (nab-paclitaxel) has been approved for the treatment of metastatic breast cancer. There are >900 ongoing clinical trials involving nab-paclitaxel as an anticancer agent, based on Clinicaltrials.gov as of August 2020. Moreover, nab-paclitaxel, in combination with 5-chloro-2.4-dihydrooxypyridine, tegafur and oteracil potassium exhibited promising results when used for the treatment of HER2-negative breast cancer patients. Doxorubicin, daunorubicin, paclitaxel and vincristine are among the most extensively investigated anticancer agents in liposome-based drug formulations. Table V provides examples of FDA approved nanomedicine

D. Nanotechnologies for the Treatment of Cardiovascular Diseases

Cardiovascular diseases are another field where the properties of nanoparticles may be leveraged. Cardiovascular diseases are the leading cause of death globally, and the rates are increasing alarmingly, due to an increase in sedentary lifestyles. Common examples of cardiovascular diseases that affect several individuals includes stroke, hypertension and restriction or blockage of blood circulation in a specific area. These diseases are the most common causes of prolonged disability and death. Nanotechnologies offer novel avenues for therapeutic and diagnostic strategies for management of cardiovascular diseases.

Most cardiovascular risk factors (for example, for hypertension, smoking, hypercholesterolemia, homocystinuria and diabetes mellitus) are associated with impaired nitric oxide (NO) endothelial production. Impaired endothelial function is established to be the first step in atherosclerosis. Gold and silica nanoparticles have been developed to improve NO supply for possible application in cardiovascular diseases, where low NO bioavailability occurs. Systemic administration of the 17-βE loaded CREKA-peptide-modified-nanoemulsion system has been shown to reduce the levels of pathological contributors to early atherosclerosis by reducing lesion size, lowering the levels of circulating plasma lipids and decreasing the gene expression of inflammatory markers associated with the disease. Moreover, novel formulations of block copolymer micelles constructed using PEG and poly(propylene sulphide) have been demonstrated to suppress the levels of pro-inflammatory cytokines, and exhibited excellent potential for management of atherosclerosis.

Drug delivery via liposomes has been proven to be effective for prevention of platelet aggregation, atherosclerosis and thrombosis. Prostaglandin E-1 (PGE-1) exhibits a wide range of pharmacological properties, including vasodilation, inhibition of platelet aggregation, leukocyte adhesion, as well as exhibiting an anti-inflammatory effect. Liposomal drug delivery of PGE-1 (Liprostin™), is currently undergoing phase III clinical trials for the treatment of various cardiovascular diseases, such as restenosis following angioplasty. Additionally, the use of liposomes carrying the thrombolytic drug urokinase has also been assessed; cyclic arginyl-glycyl-aspartic acid (cRGD) peptide liposomes encapsulated with urokinase can selectively bind to the GPIIb/IIIa receptors, and this improves the thrombolytic efficacy of urokinase by almost 4-fold over free urokinase.

Efficacy and effectiveness of the conventional thrombolytic drugs can also be advanced via novel nano-therapeutic approaches. Drugs can be selectively targeted to vascular blockage sites through mechanical activation within blood vessels based on the high-fluid shear strains present within them. In vivo and in vitro studies have been encouraging, thus validating this approach for use in lysis of blood clots, using a significantly lower amount of thrombolytic drug. One example of this technology is the use of dendrimers.

Dendrimer have been used in several diseases as a means of delivering therapeutic agents. Plasminogen activator (rtPA) has been successfully attached to dendrimers producing an alternative drug delivery system, allowing for refinement of the rtPA-dendrimer complex concentration throughout the duration of treatment using different dilution proportions of each part of the complex. Another potential role of nanoparticles is to decrease haemorrhaging, which is a severe side effect of thrombolytic agents. Targeted thrombolysis via rtPA bound to polyacrylic acid coated nanoparticles minimises the intracerebral haemorrhage, and enhances retention at the target site. Incorporation of nanotechnologies has assisted in reducing the side effects of drugs, whilst requiring lower doses of the drug to treat cardiovascular diseases. Table VI summarises some of the applications of nanoscale pharmaceuticals in drug delivery. The current progress in nanotechnology research for drug delivery systems, particularly with regard to their water-insoluble properties, has enabled drugs to be delivered to target sites with higher carrier capacity, specificity and stability. The constant advancements in nanoparticle drug delivery systems have allowed researchers to develop formulations that can increase the efficiency of drugs, whilst reducing the cost.

E. Potential risks of Nanotechnologies

Although the emerging field of nanotechnology has piqued the public's interest at large, nanotechnologies have also resulted in extensive discussions regarding their safety and any health risks associated with their use. New challenges arise with the use of nanomaterials, specifically in predicting, understanding and governing the potential health risks. Research has demonstrated that low-solubility nanoparticles are more hazardous and toxic on a mass by mass basis than larger particles. Other potential risks posed by nanoparticles include explosions and catalytic effects. It is important to note that only specific nanomaterials are considered risky, particularly those with high reactivity and mobility. Until more thorough studies can confirm the hazardous effects of nanomaterials, the mere presence of them in a laboratory setting will not in itself impose a threat to humanity and the environment. Potential risks of nanotechnology can be broadly grouped into three areas: Health, environment and society.

VII. CONCLUSION

It appears that nano drug delivery systems hold great potential to overcome 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 facilitating movement of drugs across barriers such as those in the brain. The challenge, however, remains the precise characterization of molecular targets and to ensure that these molecules are expressed only in the targeted organs to prevent effects on healthy tissues. Secondly, it is important to understand the fate of the drugs once delivered to the nucleus and to cause nanosystems increase efficiency of drug delivery, the doses may need recalibration. Nevertheless, the future remains exciting and wide open. There is no doubt that nanotechnologies have helped to improve the quality of life of patients by providing a platform for advances in biotechnological, medicinal and pharmaceutical industries. They have also facilitated healthcare procedures, from diagnosis to therapeutic interventions and follow-up monitoring. There is a constant push to create and develop novel nanomaterials to improve diagnosis and cures for diseases in a targeted, accurate, potent and long-lasting manner, with the ultimate aim of making medical practices more personalised, cheaper and safer.

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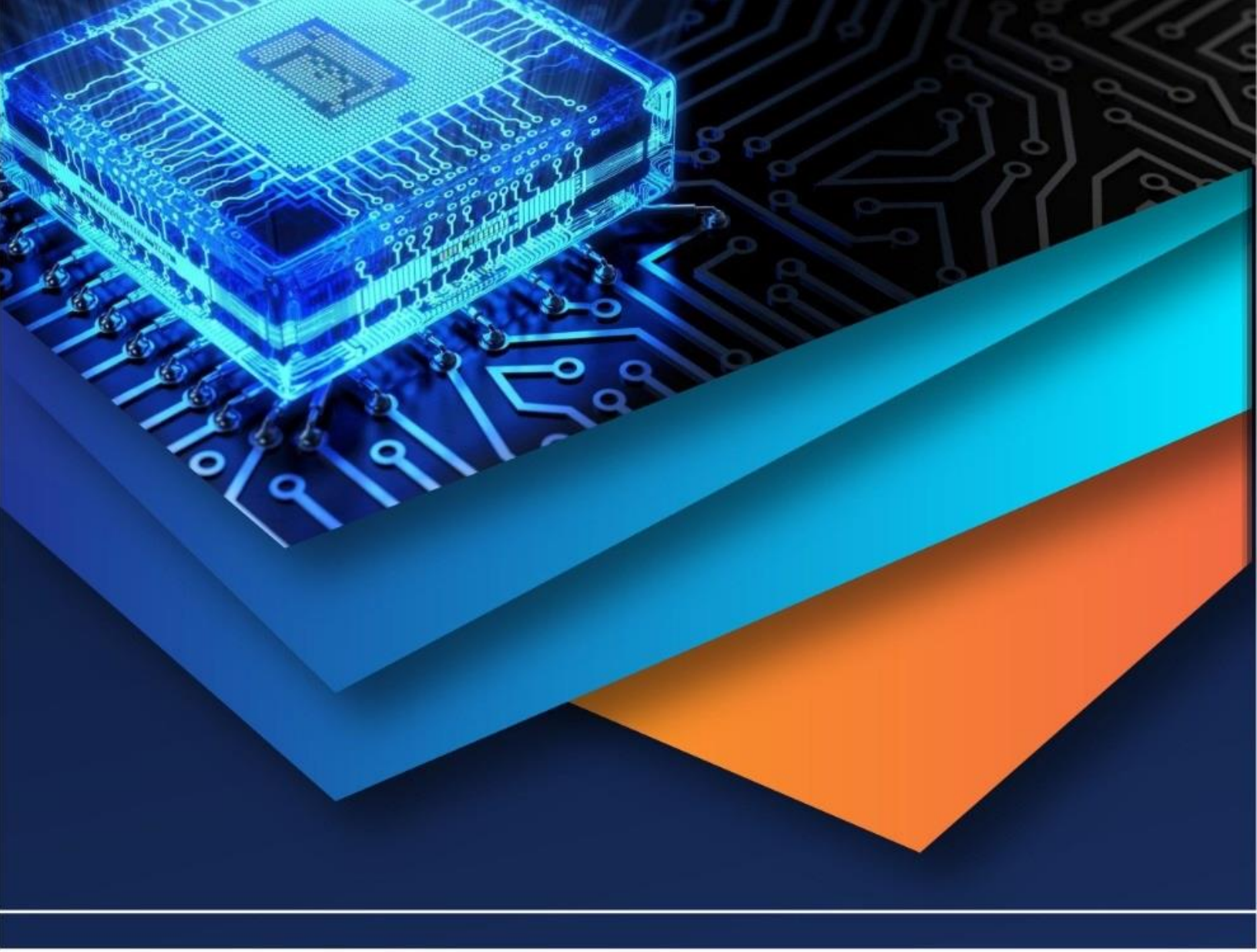

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