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Nanotechnology: A Therapeutic Approach

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ABSTRACT

Nanotechnology can be defined as the manipulation, precision-placement, modeling and manufacture of material at the nanometer scale. The purpose of this review is to discuss the impact of nanotechnology in the treatment of the major health threats including cancer, infectious diseases, metabolic diseases, autoimmune diseases, and inflammations. Indeed, during the past 37 years, the explosive growth of nanotechnology has burst into challenging innovations in pharmacology. Although the introduction of nanotechnology obviously permitted to step over numerous milestones toward the development of the magic bullet proposed a century ago by the immunologist Paul Ehrlich. Cancer cells have unique properties that can be exploited by nanoparticles. They can be used very effectively for drug delivery. Normally, drugs work through the entire body before they reach the disease-affected area. Using nanotechnology, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects. A great advantage of using nanotechnology for drug delivery is that the amount and time of drug release can be easily controlled by predetermination of nanoparticle. Nanotechnology is still in its early stages. The applications discussed in this review have already been developed and are already helping patients all over the world.

Keywords- Nanoparticle, Cancer, Alzheimer's disease, TDDS

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INTRODUCTION

Nanotechnology is the development and manufacturing of technology at a scale of a nanometer – 1×10^{-9}m. Nanotechnology is present in many parts of industry and medicine and the impact that nanotechnology is having on modern day life is growing with every year that passes. The future view of nano-manufacturing is the combination of engineering, science and biology. Nanotechnology is relevant to the advancement of Medicine because of the many ways it can be used to advance the treatment of patients.

In the past 37 years, the explosive growth of nanotechnology has burst into challenging innovations in pharmacology, which is in the process of revolutionizing the delivery of biologically active compounds. The main input of today's nanotechnology in pharmacology is that it allows real progresses to achieve temporal and spatial site-specific delivery. Thus, the concept of the magic bullet proposed a century ago by the immunologist Nobel laureate Paul Ehrlich turned out recently to reality with the appearance of several approved forms of drug-targeting systems for the treatment of certain cancer and serious infectious diseases.

First liposomes proposed in 1974 by Gregoriadis et al [1] and today, there was an explosion in the number of nanodevices suitable for drug delivery, which are either made of lipids or composed of polymers (Figure. 1) [2].

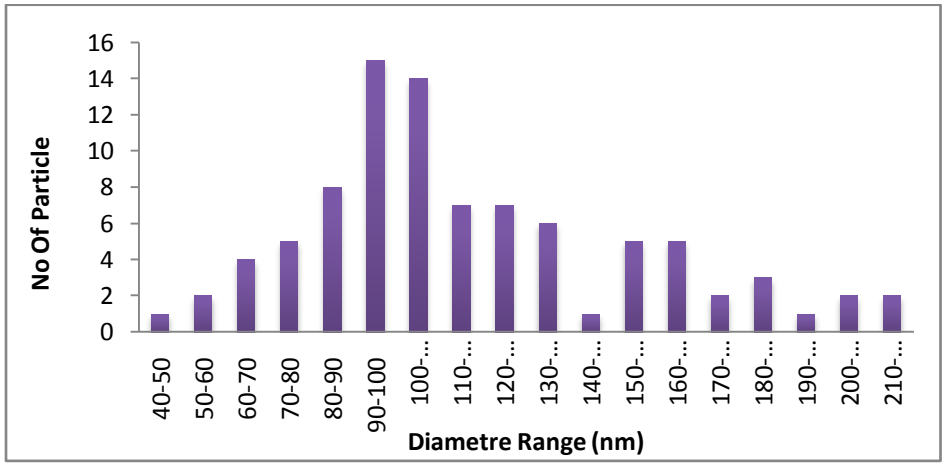

Figure1: Particle size range of nanopartical

Recently, new drug delivery systems based on carbon assemblies were also suggested. These systems are exploited for therapeutic purpose to carry the drug in the body in a controlled manner from the site of administration to the therapeutic target. This implies the passage of the drug molecules and drug delivery system across numerous physiological barriers, which represent the most challenging goal in drug targeting [3]. In general, nanocarriers may (i) protect a drug from degradation, (ii) enhance drug absorption by facilitating diffusion through epithelium,

(iii) modify pharmacokinetic and drug tissue distribution profile, and/or (iv) improve intracellular penetration and distribution (Table I). Nanosystems were also found useful to improve the performance of imaging techniques applied for the in vivo diagnosis of tumors.

Another very demanding field includes infectious diseases such as Human immunodeficiency virus (HIV), Leishmaniasis, Malaria, Nosocomial infections, all kinds of infections in immunocompromised patients, etc. with already approved drugs for clinical uses (Ambisome) (4). The impact of nanotechnology in pharmacology to improve treatments of various diseases considered as the major health threats (cancer, infections, metabolic diseases, etc.

Mode of Drug Delivery In Nanotechnology

Liposomes

Liposomes are small artificial vesicles of spherical shape that can be produced from natural nontoxic phospholipids and cholesterol[5]. Forming lipid bilayers through hydrophobic interaction, liposomes are considered as excellent platforms for the delivery of hydrophobic and hydrophilic drugs. In particular, liposomes present considerable persistence in the blood. It facilitates efficient drug delivery to target tissues. Liposomes are particularly useful as gene therapy devices because of their ability to pass through lipid bilayers and cell membranes, and several groups have recently reported convincing results following local delivery[6]. Transferrin (Tf)-lipoplex has demonstrated high efficiency in tumor-targeted gene delivery and long-term therapeutic efficacy in systemic p53 gene therapy in humans for both head and neck cancer and prostate cancer[7]. Commercial liposomes have already gained approval from US Food and Drug Administration (FDA). The typical example is doxorubicin encapsulated liposomes (Doxil), which has strong antitumor activity against a wide range of cancers.

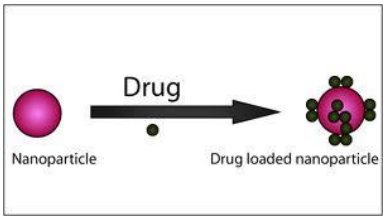

Figure2: Nanoparticle loading drug

Nanoparticles

Nanoparticles are colloidal particles having a size of 10 to 1000 nm [8]. Nanoparticles and microparticles formulated using PLGA and PLA polymers are being investigated as a nonviral gene delivery system because of their sustained-release characteristics, biocompatibility, biodegradability, and ability to protect DNA from degradation in endolysosome. Greater gene

transfection than those formulated using PLA polymer in breast cancer (MCF-7) and prostate cancer cell lines (PC-3), and this was attributed to the higher DNA release from PLGA nanoparticles [9]. Cells that were transfected with naked DNA demonstrated transient intracellular DNA retention Studies with fluorescently labeled DNA using confocal microscopy and quantitative analyses using a microplate reader demonstrated sustained intracellular localization of DNA with nanoparticles, suggesting the slow release of DNA from nanoparticles localized inside the cells. Cells that were transfected with naked DNA demonstrated transient intracellular DNA retention [10].

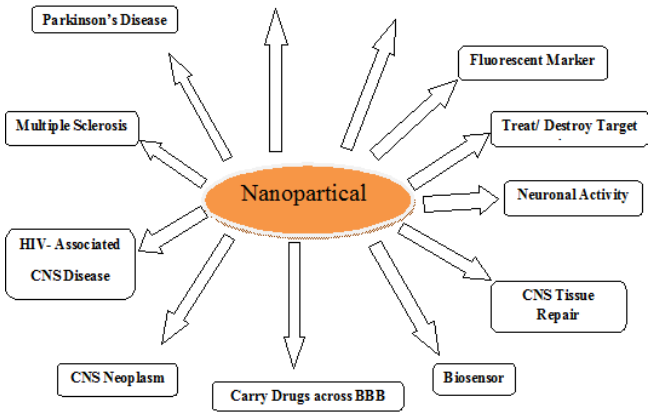

Figure 3: Nanotechnology in drug delivery and treatment

Table I. Therapeutic Challenges Addressed with Nanotechnology to Improve Treatment against Major Human Health Threats

Disease	Therapeutic challenge	Nanotechnology solution
Cancer	Increase efficacy, Reduce toxicity By Controlling biodistribution, Improving intracellular penetration, PEGylated micelles, Targeted nanoparticles, Targeted liposomes	Nanoparticles ,Liposomes Micelles, PEGylated nanoparticles, PEGylated liposomes
Infections	Increase efficacy, Reduce toxicity By Controlling biodistribution, Improving intracellular penetration (in macrophages, cell-presenting antigens, dendritic cells.) , Facilitating absorption through mucosa, Improving protection against degradation (antigenic peptide)	Nanoparticles, Liposomes, PEGylated nanoparticles, PEGylated liposomes, Antigen-presenting devices
Metabolic diseases	Protection against degradation(therapeutic peptides and proteins)	Nanopartical, Liposome
	Improve mucosal absorption, Controlled and sustained release	Nanopartical, Liposome
Autoimmune disease, prevention	Control biodistribution to target the immune system and/or the inflammatory Controlled and sustained release	

of graft rejection	PEGylated nanoparticles PEGylated liposomes	
Pain treatment	Controlled and sustained release Improve the bioavailability towards the central nervous system (CNS)	Liposomes CNS targeted liposomes CNS targeted Nanopartical Solid lipid nanoparticle
Gene therapy relate diseases	Protect against degradation Condense DNA Improve cellular uptake Address cytoplasmic/nucleus intracellular compartments Nanocapsules.	Cationic nanospheres Cationic polymers Cationic lipids Cationic nanogels

Dendrimer

As highly branched artificial macromolecules with treelike structures, dendrimers are monodisperse, Three dimensional molecules which have defined molecular weights and hosteguest entrapment properties with the size ranging from 1 to 10 nm, dendrimers with different chemical structures and functional groups can be synthesized [11]. The key useful character of dendrimers is the branches which can provide vast amounts of surface area for drugs and targeting molecules. Polyamidoamines (PAMAMs) are the most often used and characterized dendrimers for gene delivery, and several groups have recently demonstrated their efficacy. Intravenous administration of the complex showed transgene expression in the lung with peaks at 12 to 24 hours and 3 to 5 days.

Nanoshells

As the layer by layer assembly of nanoparticles, polymeric nanoshells (2060 nm) of diblock copolymers can be made by self assembly of oppositely charged polymers forming a core/shell structure. Gold nanoshells (10 to 300 nm) are optically tunable nanoparticles comprising a dielectric core with a thin gold shell surrounded[12]. Laser activated gold nanoshells thermal ablation is a selective and effective technique for the ablation of prostate cancer in an ectopic tumor model [13].

Superperamagnetic Nanopartical

Super paramagnetic nanoparticles, iron oxide magnetic nanoparticles with particle sizes of about 20 nm, are composed of Fe_2O_3 or Fe_3O_4 and do not keep any magnetism after removal of the magnetic field, hence, may be used in vivo[14] . Super paramagnetic nanoparticles can be used as contrast agents for magnetic resonance imaging (MRI), can be used for cancer thermal therapy, and can concentrate in target sites through an external magnetic field.

Carbon Nanotube

As a distinct molecular form of carbon atoms which bond with each other via sp^2 bonds and

present a hexagonal arrangement, carbon nanotubes were first discovered in the late 1980s[15]. Carbon nanotubes are described as well ordered, hollow nanotubes formed when single or multiple graphene sheets are rolled into a cylinder. The two forms of carbon nanotubes are single and multi walled carbon nanotubes. Carbon nanotubes can immobilize molecules, such as antibodies, DNA and drugs, in order to penetrate cell membrane. Recently, the biological impacts (cytotoxicity, DNA damage, and inflammation) induced by different sized. Multi walled and single walled carbon nanotubes have been studied.

APPLICATIONS OF NANOTECHNOLOGY IN PHARMACOLOGY

Cancer

Nanotechnologies for the delivery of small anticancer molecules. Even if new molecules are discovered to treat cancer diseases, the clinical use and efficacy of conventional chemotherapeutics is hampered by the following limitations: (i) drug resistance at the tumor level because of physiological barriers (noncellular-based mechanisms); (ii) drug resistance at the cellular level (cellular mechanisms); and (iii) distribution, biotransformation, and clearance of anticancer drugs in the body.

At the tumor level, for example, the high interstitial pressure may lead to an outward convective interstitial fluid flow, which opposes to the diffusion of the drug molecules from the vascular space to the tumoral tissue, the drug transport being governed also by the physicochemical properties of the interstitium (composition, structure, charge) and of the molecule itself (size, configuration, charge, hydrophobicity) [16]. It is therefore of importance to develop new nanotechnologies (liposomes, nanoparticles, polymerized micelles, etc.) for targeted delivery to tumors both at the cellular and tissue levels, thereby improving the therapeutic index of the carried anticancer molecules. This biodistribution can be of benefit for the chemotherapeutic treatment of mononuclear phagocyte system (MPS) localized tumors (e.g., hepatocarcinoma or hepatic metastasis arising from digestive tract or gynecological cancers, bronchopulmonary tumors primitive tumors or metastasis including nonsmall cells tumor and small cells tumors, myeloma, and leukemia)[17]. the reduction in the number of metastases was much greater with doxorubicin-loaded nanoparticles than with free doxorubicin, particularly if the treatment was given only when the metastases were well established.

Recently, a great deal of work has been devoted to developing so-called Stealth particles, which are invisible to macrophages (Stealth is a registered trademark of Liposome Technology Inc., Menlo Park, CA, USA)[18]. Thus, those second generation of Stealth nanotechnologies with small size and/or decorated with hydrophilic polymers (PEG, poloxamers, hydrophilic polysaccharides,

etc.) are able to selectively extravasate in tumors with a leaky vasculature. The mechanisms by which those Stealth nanotechnologies diffuse into the tumors and release their drug content are not completely understood. It is believed that these nanosystems need to be small enough and to circulate for a sufficient period of time to extravasate selectively through the small defects of the fenestrated and leaky vasculature that generally characterize tumor vessels[19]. This so-called Enhanced permeability and retention effect results in intratumoral drug accumulation, which is even higher than that observed in plasma and other tissues. Doxil formulation in which a PEG layer surrounds the doxorubicin-containing liposomes (100nm). Doxil has been investigated in various cancer types including breast cancer, ovarian cancer, non-Hodgkin's lymphoma, nonsmall cell lung cancer, etc. In the USA, Doxil is approved by the Food and Drug Administration for the treatment of metastatic ovarian cancer in patients with diseases refractory to both paclitaxel and platinum-based chemotherapy regimens, and it may be considered as a drug of choice for patients with advanced ovarian cancer for whom first-line chemotherapy has failed[20].

Infectious Diseases:

The discovery of novel molecules is probably the leading strategy in finding new treatments for infectious diseases. However, these active molecules need to reach, at the cellular /subcellular stage as well as at the tissular level, the exact site in the body where pathogens are hidden.

Fungus and Parasite Infections-

Systemic delivery of antibiotics with liposomes was extensively investigated against parasites responsible for severe infections including visceral leishmaniasis, candidose, and malaria[21]. In general, liposomal formulations seemed superior for the treatment of all kinds of infections (i.e., fungal, parasite, bacterial, viral) compared to treatment with the free drug. The efficacy of the treatment was also improved by increasing the dose that can be administered to patients because of the safety profile of the liposomal formulation. For instance, after formulation in liposomes, toxicity of amphotericin B, which is the leading compound against leishmaniasis and fungus, was reduced by a factor of 50- to 70-times [22.] This allowed the administration of more than 5-times of the drug compared with conventional treatments. The success of this formulation is also because of the small size of the liposomes making the Ambisome particles (<100 nm). This allows a large portion of the injected dose to escape immediate clearance by the macrophages of the liver and the spleen. Ambisome is now considered as an excellent treatment for visceral leishmaniasis, and it has been proposed for many other therapeutic indications as far as fungal infections are concerned [23]. In the case of malaria, the chloroquine-loaded liposomes could even

cure chloroquine-resistant infections. Long circulating formulations including PEG-coated liposomes and nanocapsules also seemed superior to the free drug to treat malaria. Halofantrine is one of the new antimalarial molecules developed because of the emergence of chloroquine resistance P. falciparum.

Bacterial Infections

Nanotechnologies are also attractive candidates for the delivery of antibiotics in infections Caused by bacteria. Generally, the encapsulation of antibiotics in liposomes or in nanoparticles increased the maximal tolerated dose and the therapeutic index of the antibiotics compared with the free drug[24]. In a liposome formulation of amikacin (Mikasome, Gilead), which is in clinic evaluation, the antibiotic was found 2- to 6-fold more active than the free drug. So far, most of the very promising data were obtained by treating experimental animal infections with antibiotics associated with nanodevices in comparison with the free drug.

Viral Infections

Viral infections are caused by noncellular agents. They are probably the most difficult infections to treat, and finding suitable efficient therapies requires new resources. Thus, liposomes and nanoparticles were proposed as sustained released formulations to improve intravitreal treatment with AS-ON [25.]

Vaccines-vaccinology is the way antigens are presented to the immune system. The use of nanotechnology was suggested to resolve some of the problems that emerged with novel antigens produced by biotechnology or following innovative vaccine approaches. Adjuvants based on nanotechnology were developed as early as in the 1970 using liposomes and nanoparticles. They were first proposed as encapsulation method to simply insure protection of protein antigens against degradation by peptidases prior to their uptake by macrophages [26] Today, the immunoadjuvant role of liposomes and nanoparticles is much wider. For instance, the new marketed hepatitis, Epaxal and influenza, Inflexal, vaccines (Berna Biotech, Zurich, Switzerland) are formulated with virosomes, which correspond to a new technology platform consisting of a liposomal carrier for antigens. a recent therapeutic vaccination approach developed against the chronic hepatitis B virus suggested to target the induction or the stimulation of CD4+ and CD8+ T-cell responses and the induction of proinflammatory cytokines capable of controlling viral replication[27].

Metabolic Diseases:

Metabolic diseases include several major public health threats. For example, diabetes concerns approximately 150 million patients worldwide, and osteoporosis is the most prevalent metabolic

bone disease. However, mucosal routes are extremely challenging for the administration of peptides and proteins because these generally hydrophilic macromolecules are unable to overcome mucosal barriers by themselves and are degraded before they can reach the blood stream. Liposome technology was introduced as early as 1976 with the primary aim to protect insulin against proteolysis degradation in the gastrointestinal tract [28]. Nanoparticle technology was, then, proposed for the first time in 1988 for successful oral delivery of insulin [29]. Polymer nanoparticles were the subject of considerable experiments especially for the delivery of proteins by the oral and nasal routes. It was demonstrated that particles of size below 1 mm in diameter can be absorbed across the intestinal epithelium after oral administration and can be used to transport peptides and proteins across the barrier. For example, poly (alkylcyanoacrylate) nanocapsules resisted well in the gastric fluid retaining the encapsulated insulin inside the nanocapsules. In the intestinal medium, the nanocapsule envelope can be degraded by intestinal esterases, and most of the encapsulated insulin can be released in less than 30 min[30].

Parkinson's disease

Parkinson‟s disease is a progressive neurological condition. Nanotechnology is being applied ingeniously to provide new, patient-friendly solutions to delivering drugs. Delivering a drug correctly, to the right part of the body, causes numerous challenges. Drugs used in the treatment of Parkinson‟s disease e.g. Levodopa, sometimes have limited solubility and may break up before reaching their intended destination. Drugs may also distribute unsuccessfully or inadvertently cause damage to healthy tissues. Researchers are looking into how nanotechnology could maintain drug levels within the therapeutics range; achieve effective targeting to the intended site of drug delivery, carry out slow release and decrease toxicity and side effects of drugs. These advantages include; high stability, the possibility of transporting both hydrophilic and hydrophobic drugs, high carrying capacity due to greatly increased surface area, better bioavailability, systems that allow controlled release rates or release upon an external stimulus and the possibility to exploit a range of patient-friendly delivery routes.

Alzheimer's disease

Alzheimer's disease (AD), first described by Alois Alzheimer in 1907, is the leading cause of dementia, accounting for more than half of all dementias in old age. The currently available therapeutics for AD, only act to lower its symptoms ,In recent years, however, significant amount of research have been focused on finding the so called "neuroprotective" agents, therapeutics that can stop the disease progress by targeting special molecular mechanisms in the AD pathology process. Yet more futuristic are approaches that can rebuild the damaged tissue,

called as "regenerative agents". These two approaches together are known as "disease-modifying approaches". The therapeutic potential of nanotechnology for AD includes both neuroprotective and neuroregenerative approaches.

The main two sources of neurotoxicity in AD pathogenesis are Aβ oligomers and free radicals. Some of the nanotechnology-based approaches are capable of protecting neurons from Aβ toxicity by preventing from amyloid oligomerization (*anti-assembly* strategy) and/or accumulation of Aβ oligomeric species. The other nanotechnology neuroprotective approaches include those that protect neurons from oxidative stress of free radicals [31].

OTHER APPLICATIONS

Autoimmune Disease and Prevention of Graft Rejection

Liposomes improved the intraocular bioavailability of cyclosporin A without showing toxicity on the retina. Using chitosan nanoparticles, therapeutic concentration of cyclosporin A could be maintained for at least 48 h at the ocular surface, mainly in the cornea and the conjunctiva. Among the different types of nanoparticles that were evaluated, those made of chitosan presented the highest performance for the delivery of cyclosporin A in the periocular tissue, together with a good ocular tolerance. It is interesting to point out that it is now possible to design nanotechnology able to target different regions of the eye allowing, for instance, the precise delivery of cyclosporin A to the intraocular compartment for the treatment of the ocular uveitis or to the external tissues for the treatment of extraocular diseases, such as the keratoconjunctivitis sicca. Several other compounds were combined with Nanoparticles to control the progression of autoimmune diseases. The current treatments of glaucoma with pilocarpine or betaxolol may be improved using nanotechnologies too.

Inflammation

One of the main drawbacks of the major anti-inflammatory agents, diclofenac and indomethacin, is their local toxicity in contact with tissues. They induce ulcers on the gastrointestinal mucosa when they are administered by the oral route and cause damage on the corneal epithelium after instillation or on the muscular tissue after intramuscular injection. The local toxicity can be considerably reduced by encapsulation into nanocapsules or in liposomes while the pharmaceutical activity of the nanoencapsulated drug was not influenced by the encapsulation [32].

Pain

Quite recently, liposomes have attracted much attention for pain management, mainly to develop sustained released delivery systems for anesthetic compounds. They are then used either by topical administration [33] or by single injection at the time of surgery. For local anesthesia

achieved by topical administration, the liposomal formulation (lidocaine, tetracaine) is incorporated in a cream and applied onto the skin surface at the place where the anesthesia is needed. The liposomal formulation of morphine proposed today for postoperative pain management consists of an extended release of morphine for epidural administration. The liposome technology used consists of lipid-based particles with closely packed internal chambers separated by lipid membranes (Depofoam, SkyePharma, Inc., San Diego, CA, USA) containing the drug. Apart from liposomes, a very recent study suggested the use of solid lipid nanocapsules containing ibuprofen for pain management [34].

Oxygen Carriers

Nanosystems were thought to be useful to develop artificial erythrocytes for blood substitute. The main indication would be the rapid supply of hemoglobin when blood is not available after excessive blood loss because of an accident or surgery. The main advantage of these nanosystems is their immediate availability after wounding without need for special storage conditions. Haemoglobin-based oxygen carriers were developed by encapsulating the haemoprotein in liposomes [35], nanocapsules, or by loading into nanoparticles.

RESULT AND CONCLUSIONS

The introduction of nanotechnology in pharmacology has revolutionized the delivery of drugs, allowing the emergence of new treatments with an improved specificity. Nanotechnology is now widely implanted in the move of revisiting drug delivery methods. They can be administered by all routes of administration for systemic or local treatments. Their values are the control of the drug release and distribution, the enhancement of drug absorption (by mucosa or cells), and the protection of drugs from degradation. Next improvements will certainly come from the introduction of new materials including stimuli-responsive polymers to elicit the challenge of targeting the drug to its specific site of action, to retain it for the desired duration, and to release it according to the correct time schedule.

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