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DIFFERENT SHADES OF NANOTHERAPEUTICS

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ABSTRACT

Research and development of innovation drug delivery system are increasing at rapid pace throughout the world. The major factors that determine the treatment outcome in a patient are the efficacy and safety profile of drug so new therapies with increased efficacy and minimal toxicity are of utmost need for better public health. For that one, important aspect is development of wide spectrum of nanoscale technologies which allow innovative therapeutic approaches and laid the foundation of Nanomedicine. Nanomedicine comprises of three main subsections Nanotechnology, nanobiotechnology and nanobiomimetics. The spirit of this combinational attribute allows nanomedicine to crowned with the little of "revolutionary interdiscipline." There are many innovative plateform of nanotherapeutics; mainly systems based on lipid or polymeric nano particles. Today many drug delivery system based on nanotechnology are in market like cancer, AIDS, fungal infection, viral infection, gene therapy even for diagnostic purposes and orthopedic biomaterial. These smart multifunctional nanoparticle delivery devices can be value-added for optimized therapeutic activity and lead to development of safer, precise and less intrusive form of medical practice i.e. personalized medicine. Nanoparticles are also associated with potential pitfalls or undesirable side effect. They are hazardous for health and ecosystem. Approaches should be done to design safer nanotherapeutics by carring out toxicity study and by setting safety profile of nanoparticles.

Keywords: Nanoparticle, Nanotechnology, Applications.

INTRODUCTION

The term 'nano' is a Greek word for dwarf. In science it mean one billionth of anything. So one nanometer is 1 billionth of a meter. In the 1980s, K.Eric Drexler popularized the word' nanotechnology' His idea was to build machines on the molecular scale.[1] Most of the fundamental biological functions occur at molecular level that have size range of less than 100nm. Nanotechnology is creation of nanomaterials with remarkably varied and new properties by manipulation of matter at atomic and molecular level. [2] The application of nanotechnology to the medical sector is referred to as Nanomedicine. Nanomedicine interrelate three main subsections Nanotechnology, Nanobiotechnology and nanobiomimetics. Nanoparticle engineering refered to as nanotechnology and exploitation of nanotechnology over biological entities for the application to medicine is termed as nanobiotechnology. Biological studies focused at nanoscale level are termed as Nanobiology. [3] Designing and Synthesis of nanomaterial which utilizes the biogical structure and mechanism is known as Nanobiomimetics. Protypical example of it is molecularly imprinted polymers or MIPs that serve the same purpose as monoclonal antibodies.[4,5] Nanopharmacology is the application of nanotechnology in development of nanomedicine to improve therapeutic efficacy and reduce side effects for that it deals with discovery of new drug entities suitable drug carriers and selection of pharmaceuticals. This is achieved by selective delivery of drug molecule to the target site in the body and by sparing normal tissue. [6]

Applied in almost all branches of medicine i.e all sort of preparations are available ranging from intravenous to ophthalmic preparations. [7] Moreover, Nanoparticles are double edge sward. Besides providing promising result in terms of efficacy they have potential for toxicity over human health and also over environment. This area of research created another scientific discipline in nanotechnology termed nanotoxicology. [8]

Nanocarriers

Nanoparticles are solid, colloidal particles consisting of macromolecular substances varying in size from 10 to 1000 nanometers. According to the process used for the preparation of nanoparticles they are of two types Nanosphere and Nanocapsules [9]. Nanoparticles act as carriers for conventional drugs as well as for peptides, proteins, enzymes, vaccines and antigens. The drug can be dissolved, entrapped, adsorbed attached or encapsulated into nanoparticles. Nanocarries for pharmaceutical use can be of polymeric natures or consist of lipophilic components plus surfactants i.e. liposomes, niosomes and solid lipid nanoparticles, other material investigated for nanoparticle preparation are albumin, gelatin or calcium alginate, collegen, chitosan [10]. Biodegradable polymers used for their preparation provide sustained drug release at the targeted site over a period of days and even week after administration. [11].There are many inovative nanotechnology platform used not only for therapy as well as for diagnosis e.g Quantam dots, Fullareness, colloidal gold, carbon nanotubes, nanoshells and nanowires. Nanotechnology has the potential to improve the whole care process that start for a patient once a disease is suspected, from diagnosis to therapy and follow-up monitoring.

Table 1: List of FDA approved Nanoparticles delivery system [12]:

Trade Name	Active Ingredient	Indication*	Manufacturer	Approval
Abelcet	Liposomal Amphotericin B	Invasive Fungal Infections	SigmaTau	1995
Abraxane	Albumin protein bound Paclitaxel	Metastatic breast cancer	Celgene	2005
Adagen	Pegylated adenosine deaminase enzyme	Severe Combined Immunodeficiency disease	Sigma Tau	1990
Allmta	Pemetrexed	Nonsquamous small cell carcinoma of lung	Lilly	2004
AmBisome	Liposomal amphotericin	Fungal infection Leishmaniasis	Astellas/Gilead	1997
Amphotec	Liposomal amphotericin	Invasive aspergillosis	Alkopharma	1996
Cimzia	Pegylated fab fragment of a humanized anti-TNF –alpha antibody	Crohn's disease rheumatoid arthritis	UCB	2008
Copaxone	Glatiramer acetate	Multiple Sclerosis	Teva	1996
Daunoxome	Liposomal daunorubicin citrate	HIV-associated Kaposi's Sarcoma	Galen	1996

Depocyt(e)	Liposomal cytosine arabinoside	Lymphomatous meningitis	Pacira	1999
Doxil	Pegylated-stabilized liposomal doxorubicin	AIDS-related Kaposi's Sarcoma, Multiple myeloma	Janssen	1995
Ellgard	Leuprolide acetate and PLGH-polymer formulation	Advance prostate cancer	Sanofi	2002
Emend	Aprepitant nanocrystal particle	Chemotherapy related nausea and vomiting	Merck	2003
Macugen	Pegaptanib (PEG-anti- VEGF aptamer)	Wet age- related macular degeneration	Eyetech	2004
Mircera	Methoxy-PEG-epoetin	Symptomatic anemia associated with CKD	Hoffman La Roche	2007
Neulasta	Pegfilgrastim	Chemotherapy associated neutropenia	Amgen	2002
Oncaspar	PEG- asparaginase	Acute lymphocytic leukemia	Sigma Tau	1994
Ontak	Interleukin-2 diptheria toxin fusion protein	Cutaeuos T-cell lymphoma	Eisai	1999
Pegasys	Peginterferon alpha-2a	Hepatitis Band C	Genentech	2002
Pegintron	Peginterferon alpha-2a	Hepatitis C	Merck	2001
Renagel	Amine-loaded polymer	Serum phosphorus control in patient with CKD on dialysis	Genzyme	2000
Somavert	Pegylated human growth hormone receptor antagonist	Acromegaly	Pfizer	2003
Tricor	Fenofibrate	Hypercholesterolemia , mixed dyslipidemia	Abbott	2004
Visudyne	Verteporfin	Wet age related macular degeneration	QLT ophthalmics	2000

Application in cancer therapeutics

Cancer is one of the most deadly diseases that affect humans. Many researches are going on pathophysiology and there is an impressive advance in pathogenesis of cancer and at metastatsis level. Still the therapy is widely debated in term of maximum efficacy and minimum toxicity. Thus there is critical need not only for specific effective therapies without side effects, but also mechanisms for early detection to ensure precise and effective therapy.

Drug delivery to target tissue achieved by two ways i.e. Active and passive. Passive targeting can be accomplished by taking advantages of permeability of tumor tissue, its microenvironment and by direct local application at tumor site. Heavy vascularisation at tumor tissue facilitates entry of chemotherapeutic drug at target site. So concentrations of polymer-drug conjugates in tumor tissue can reach to high level. Tumor microenvironment can convert some inactive chemotherapeutic drugs to active one, for example: albumin bound doxorubicin can be efficiently cleaved by matrix-metalloproteinase-2 present at tumor site and liberates free doxorubicin [13]. Drug can also be delivered to tissue bed by direct local application.

Active tissue targeting (Figure 1) for drug delivery can be achieved by conjugating nanoparticle with a ligand against tumor tissue carbohydrate, receptor and antigen present on tumor cell surface. Ligand conjugated nanocarrier with drug molecule when reaches to tumor tissue it get attached to receptor present over tumor tissue surface and then get internalized by receptor mediated endocytosis. Tumor cell cleave the drug molecule from nanoparticle and made it free to perform action within tumor cell only thus avoid the normal cell [14]. Like polymeric nanoparticle loaded with camptothecin when conjugated with folates showed better results in terms of efficacy and toxicity for folate-receptor-positive cancer cells. [15]

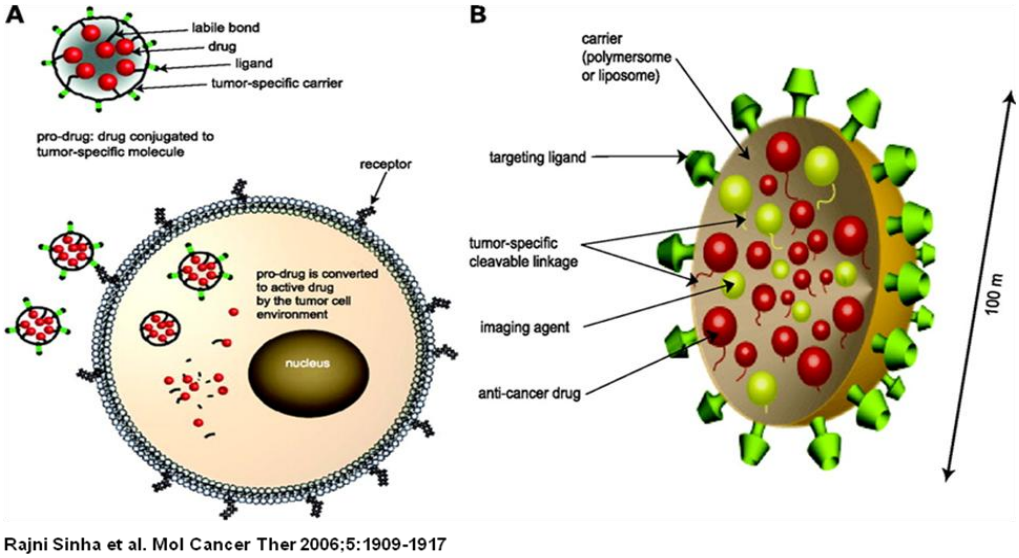

Figure 1: Active targeting for drug delivery.

Nanotherapeutic for orthopedics

Nanotechnology utilization on implanted interfaces tissue engineering and therapeutics now become part of orthopaedic research. Much work had been done for improved drug delivery to bone via nanocarrier. Betamethasone sodium phosphate loaded nanospheres showed enhanced duration of action when compared to simple betamethasone solution. [16] Topagraphic modification at nanoarchitectural level could contribute to cell surfaces interaction characterstics. It has been investigated that substitution of strontium for calcium on hydroxyapatite can have enhanced osteoblast proliferation and function with decreased osteoclast formation.[17] Xin et al have produced strontium-releasing nanotube arrange on the surface of titanium implants

they are capable of releasing strontium at slow rate leads to prolonged action [18]. It has been found through tissue engineering titanium-blast implants coated with nanostructured calcium when placed into rabbit tibia demonstrated greater bone-implant contact lead to enhanced osteointegration [19]. Xiong and Gao succeded in forming synthetic articular cartilage by nanohydroxyapatite reinforced polyvinyl alcohol [20].

Renal/Cardiovascular application of Nanopharmacology

Nanopharmacology could also have potential to improve treatment protocol in renal and Cardiovascular diseases [21, 22, 23]. Wang et al investigated drug eluting coating consisting of magnetic mesoporous silica nanoparticles and carbon nanotubes are biocompataible alternative to drug- eluting stents. A dendrimers for Angiotensin type 1 receptor SiRNA in rat ischema-reperfersion model was found to improve cardiac function recovery. The revolutionary treatment for cardiovascular and renal disease is expected to result from this burgeoning field [24].

Nanotherapeutic for ophthalmology

Eye is a tiny and delicate organ of body. There are many layer of biological barriers that separates eye from other organ of body. The most important biological barrier present as tight junction of corneal epithelium and at mucosal surface that protect this delicate organ from environment or by xenobiotics. For delivery of drugs these barrier should be crossed or bypassed. To overcome this barrier several strategies including the preparation of viscous solution, prepartion with increased bioavai1ability, nanoparticles and hydrogels have been investigated [25, 26, 27, 28, 29, 30, 31]. An ideal ocular drug delivery system should possess key properties that include: (I) a controlled and sustained release profile to maintain a therapeutic concentration of the drug over a prolonged period of time to reduce the frequency of administration; (II) specific targeting and prolonged retention in the diseased tissues to improve therapeutic efficiency and mitigate side effects; and (III) patient-friendly delivery routes that minimize or eliminate side effects resulting directly from these administration methods. At present, nanocarrier-based ocular drug delivery systems appear to be the most promising tool to meet the primary requirements of an ideal ocular delivery system [32].

Nanotherapeutic for Central nervous system

More than 98% of pharmaceutical small-molecule drugs (Pardridge, 2001) [33] and all largemolecule have restricted entry in brain because of blood brain barrier. Only small (<5000Da), lipid-soluble, electrically neutral molecules and weak bases are able to diffuse passively across the blood brain barrier (BBB). Therefore, significant research is dedicated to develop methods and technologies to circumvent the BBB for brain drug delivery [34]. Nanoparticles may cross the BBB either by passive diffusion or receptor mediated endocytosis. Many research is going on for development of capable delivery candidates. In one study radiolabeled polyethylene glycol (PEG)-coated hexadecylcyanoarcylate nanospheres have been tested for their ability to target and accumulate in a rat model of gliosarcoma. Nanoparticle-mediated delivery of doxorubicin is being explored in a rodent model of glioblastoma [35, 36]. Importantly, recent work in a rat glioblastoma model revealed significant remission with minimal toxicity, setting the stage for potential clinical trials [36]. In other work, PEG-treated polyalkylcyanoacrylate nanoparticles were shown to cross the BBB and accumulate at high densities in the brain in experimental autoimmune encephalomyelitis [37], a model of multiple sclerosis [38, 39]. Ideally, methods for crossing the BBB will complement other nanotechnological tools being developed to study the CNS, including quantum dot labeling and imaging [40].

Nanotherapeutic for AIDS

Nanosystems used for HIV therapeutics offer some unique advantage like enhancement of bioavailability, water solubility, stability, and targeting ability of antiretroviral drugs. The use of nanotechnology systems for delivery of antiretroviral drugs has been extensively reviewed by Nowacek et al. and Amiji et al. [41, 42,43]. In this section, we only highlight a few of the most recent and significant examples of nanotechnology-based drug delivery. In a recent study based on polymeric systems, nanosuspensions (200 nm) of the drug rilpivirine (TMC278) stabilized by polyethylene-polypropylene glycol (poloxamer 338) and PEGylated tocopheryl succinate ester (TPGS 1000) were studied in dogs and mice [44]. A single-dose administration of the drug in nanosuspensions resulted in sustained release over 3 months in dogs and 3 weeks in mice, compared with a half-life of 38 h for free drug. These results serve as a proof-of-concept that nanoscale drug delivery may potentially lower dosing frequency and improve adherence. Lymphatic tissue largely affected by HIV, Macrophages, which are the major HIV reservoir cells, these have various receptors on their surface such as formyl peptide, mannose, galactose and Fc receptors, which could be utilized for receptor-mediated internalization. The drug stavudine was encapsulated using various liposomes (120–200 nm) conjugated with mannose and galactose, resulting in increased cellular uptake compared with free drug or plain liposomes, and generating significant level of the drug in liver, spleen and lungs [45,46,47]. Although the early efforts have not reached clinical trials yet, the works so far provide encouraging evidence that a subset of these preclinical technologies may enter clinical evaluation in the future.

Nano Toxicology

Nanotechnolgy has many clear application but with blurred consequences. Nanoscales particles posses many novel propertics such as self assembly size effects, large surface area, ultra high reactivity and quantum effects because of their very small size and unique structure. Meanwhile, rapid development of nanotechnology is likely to become new sources of human or environmental hazards through inhalation ingestion, and on skin. Nanotoxicology is defined as the study of the nature and mechanism of toxic effects of nanoscale material on living organisms and other biological systems [8]. Nano particles can induce toxicity by many ways:-

- They can generate free radicals due to phagocytic cell response and presence of transition metals. Generated free radicals can induce oxidative stress which are responsible for many diseases including diabetes, hypertension and cardiac disease.
- Oxidative stress can lead to oxidation of lipid, DNA and proteins which lead to biological damage.
- Oxidative stress can up-regulate inflammatory factors such as NF-KB, activator protein-1 and kinases which in turn lead to inflammatory process.
- Nanoparticles interact with cell, which may damage and disturb cellular function leading to production of reactive oxygen species. They may damage DNA and can induce apoptosis.
- Metabolism of nanoparticle can generate hepatotoxic metabolite.
- Nanoparticles interact with immune system and may produce immunotoxicity.
- Nanoparticles interacts with blood components and many induce haemolysis and thrombosis.[48-52]

Approaches to design safer nanotherapeutics

Size reduction would significantly increase the surface area, which in turn increases the solubility and reactivity of compound. Approaches should be to design the various size of nanoparticles and assess its toxicity in comparision with pure drug to identify the nanoparticles size range with optimum efficacy and reduced adverse effect. Identification of alternate compound with similar functionality but with toxicity is required [53, 54, 55]. Encapsulation of toxic nano compound by use of non-toxic biodegradable material will prevent exposure of toxic nanoparticle to various biological environment thereby, raduces toxicities. Moreover encapsulation provides sustain release of drug, target specific delivery with reduction in toxicity.

International bonding of ligand over nanoparticle carrier not only enhances functionality but also reduces toxicities [53].

Environmental hazard can be overcome by using zebrafish Embryos, Bacillus subtilis, Green Algae, saccharomyces cerevisiae, thus can maintain safety of engineered nanoparticles on Ecosystem. [56]

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