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# DNA based Nanocarriers for Cancer treatment

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**Abstract: -** The study aimed to achieve enhanced targeted toxicity and cell-internalization of cisplatin-loaded deoxyribonucleic acid-nanothread (CPT-DNA-NT), mediate by scavenger receptors into Hel cells. DNA-NT was developed with stiff-topology utilizing circular-scaffold to encapsulate CPT. Atomic force analysis (AFM) characterization of the DNA-NT showed uniformity among the structure with a diameter of 50–150 nm and length of 300–600 nm. The winning fabrication of the DNA-NT was confirmed through native-polyacrylamide gel activity analysis, as large the molecular-weight (polymeric) DNA-NT did not split into constituting strands beneath applied current and voltage. The results of cell viability confirmed that blank DNA-NT had the tiniest quantity toxicity at the most effective concentration (512 nM) with a viability of ninety 2 as proof of its biocompatibility for drug delivery. MTT assay showed superior toxicity of CPT-DNA-NT than that of the free CPT because of the depot unleash of CPT once DNA-NT incorporation. The DNA-NT exhibited targeted cell internalizations with the controlled living thing unleash of CPT (from DNA-NT), as illustrated in confocal photos. Therefore, in vitro toxicity assessment through flow cytometry showed enhanced programmed necrobiosis (72.7%) with CPT-DNA-NT (compared to free CPT; sixty four.4%). CPT-DNA-NT, being poly-anionic, showed enhanced endocytosis via scavenger receptors.

**Keywords: -** DNA, nanostructures, Self-assembly Nanocarriers Drug delivery, in vivo cancer treatments.

## 1. INTRODUCTION:-

Cancer is among the top causes of mortally and morbidity throughout the world.with millans of new cases reported each year. There are several methods used to treat Cancer, each one presenting with unique benefits, and side effects. The use of nanomedicine in the field of medicine has been investigated for the targeted delivery of drugs in various diseases. The main goal of nanomedicine is to overcome the drawback caused by conventional dosage forms. Platinum based therapies, such as ciplatin, are frequently used in various types of cancer. Ciplatin inhibit cancer cell growth by interfering with the transcription of the DNA in the cell. This inhibition of cellular DNA transcription causes the cell to undergo apoptosis, also known as cellular death. Nanocarriers have unique properties such as nanoscale size, hight surface to volume ratio, and favorable physicochemical characteristics. They have the potential to modulate both the pharmacokinetics and pharmacodynamics profiles of drug, thereby enhancing their therapeutic index. Loading of drug into nanocarriers can increase in vivo stability, extend compounds blood circulation time, and allow for controlled drug release. Thus, nanomedicine compounds can alter the bio distribution of drug by allowing them to accumulate preferably at the tumor site.This phenomenon is known as the enhanced permeability and retention effect (EPR) A wide range of nanomaterials based an organic, inorganic, lipid, protein,orglycan compound as well as an synthetic polymers have been employed for the development of new cancer therapeutics

## 2. WHAT ARE NANOCARRIERS:-

### 2.1 NANOCARRIERS:-

A nanocarrier is nanomaterial being used as a transport module for another substance such as a drug. Commonly used nanocarriers include micelles, polymer, carbon based material, liposome and othersubstance.

### 2.2 NANOCARRIERS: A REVIEW:-

Abstract, from the past decade, researchers have seen the potential application of nanotechnology in the field of cancer-targeted drug delivery. Nanoparticle-based chemical moieties such as polymeric based nanoparticles, dendrimers, polymersomes, liposomes, Nano micelles, metal nanoparticles, carbon nanotubes CNTs etc.

Due to their exclusive properties such as tunable surface chemistry, ability to penetract cells, stimuli-sensitization they could be designed as per the targeted tissue or cell of tumor. This review provides aninsight into the development of nanomedicine with the help of different nanocarriers for cancer/tumor-target drug delivery.

A nanocarriers is a nanomaterial being used as a transport module for another substance,such as drug SiRNA . Commonly used nanocarriers include micelles, polymer, carbon based material, liposomes and other substance.nanocarries are currently being used in drug delivery and their unique characteristics demonstrate potential use in chemotherapy.

### 2.3 KEY PRINCIPLES OF NANOCARRIERS:-

a) Targeted nanomedicine therapeutics may decrease the resistance of tumors against anticancer drugs.

b) Nanotechnology can help to improve the distribution and targeting of antitumor medication.

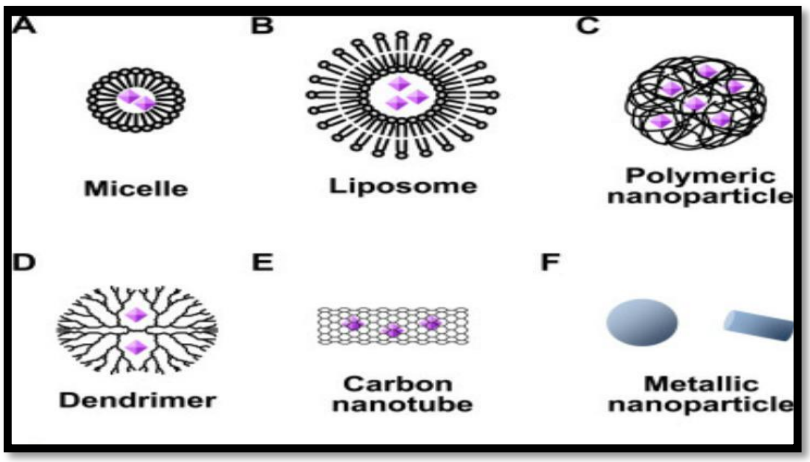
c) Nanocarriers can be designed to release their payload upon a triggle resulting in stimuli sensitive nanomedicine therapeutics.

d) The distribution of anticancer drugs is defined by their physicochemical properties and is limited by drug penetration into tumor tissue.

e) Nanoparticles may help to overcome problems of solubility and chemical stability of anticancer drugs poor water solubility limits the bioavailability of a compound and may hamper the development of anticancer agents identified during early drug screen.

**2.4 TYPES OF NANOCARRIERS: -** The nanocarriers that is applied to shield and to improve in vitro and in vivo delivery of SiRNA must be safe and non toxic for human health because they come in direct contact with humans. Naturally obtained molecules are safer as compared to chemically synthesized molecules.Because of the synthesis of NCs several hard acid and bases, and others hazardons chemical are used. This acids and hazardous chemicals give several toxic effects on human health and the environment also. Mostly NCs have the diameter>100nm. However, the long chain polymeric NCs can have the diameter>500nm. NCs developed for the systemic delivery of SiRNA can be broadly classified into three different types

**Fig 1 Nanocarriers**



**2.4.1 ORGANIC NANOCARRIERS:-**

They are four main groups of organic nanocarriers, liposome, micelles, protein or peptide based Nanocarriers and dendrimers. Organic nanocarriers (ONCs) are prepared from natural or synthetic organic molecules and the mixture of both. Organic nanocarriers are typically soft, biocompatible, biodegradable, less toxic, non immunogenic, highly stable, and can shild the SiRNA. From the last few decades, several scientist and researchers have already used numerous organic NCs for protecting the drugs and nucleic acids from the harsh environment, enzymatic degradation and blood plasma proteins during systemic circulation inside the body. The most commonly used ONCs are nanomicells, liposomes, polymeric, Nanoparticles, dendrimers and carbon Nanomaterials (graphene oxide sheets, nanotubes, spherical shape fullerene ) these NCs have same additional benefits. These NCs have same additional benefits. The synthesis procedures for ONCs are quite easy and they can encapsulate more drugs or nucleic acids molecules with a controlled delivery. The surface of ONCs can be simply decorated with targeting biomolecules to develop targeted carried systems.

**2.4.1.1 Polymeric Nanocarriers / polyplexes. :-**

Currently, several natural and synthetic polymeric Nanocarriers (PNCs) offers great platform to deliver drugs and gene with improved efficiency. These polymers are highly biocompatible, biodegradable, non toxic in nature and have outstanding controlled release character. Generally, PNCs are cationic, anionic and non ionic in nature.

Polymeric Nano gels are three dimensional (3D) Nano sized hydrogels , which are fabricated by the physical or chemical cross linking of polymers. Nano gels have attracted because of their tunable chemical and physical structures and considerable stability in vivo.

Polymers can be broadly classified into two types based on their sources natural and synthetic. The most commonly used natural polymeric chitosan (CS), poly (lactic acid-co-glycolic acid) (PLGA),atelocollagen, insulin.cs is a linear, natural, cationic.FDA (food and drug administration) approved polysaccharide (a long chain of monosaccharides carbohydrates) o-black polymer of glucosamine and N- acetylated glucosamine. Polymer and has been used for both in – vitro in- vivo systemic delivery of SiRNA Because it has nontoxicity , biocompatibility, andbiodegradability properties.

Currently, CS in the highly used polysaccharides polymer for delivering of therapeutic agents due to its high permeability capability across the semipermeable cell membrane. In one of the study prepared an novel amino acid- functionalized Arg-Gly-Asp (RGD) chitosan Nanoparticle (RGD-CHNP) that significantly increased selective intra tumoral delivery of SiRNA for regulation of many growth promoting genes (PL×DC1,FAK, and POSTN) accompanied by therapeutic efficacy in the A2780, HeyA8,and SKOV3ipl ortho topic animal studies of ovarian cancer models , Besides natural polymers, several biocompatible, biodegradable,non toxic synthesisPNCs have also been used for systemic delivery of SiRNA such as PLL,PEL,PEG dimethyamino ethyl methacrylate,polyfluorene and cyclodextfin based polycations.

These polymers are linear and branched and similarly the efficient way to shield and efficient delivery of SiRNA both types of PNCs can encapsulate a high amount of SiRNA and deliverit via the passive route.forincreasing the deliver concentration of SiRNA on specific infected cells by escaping the normal cell and tissue, different actively targeted molecules are attached to the surface of PNCs.

**2.4.1.2 Nanomicells based delivery:-**

The term ‘micelles” was given by MC Bain in 1913.micelles are formed by supra-molecular self assembly of surfactant, lipids, aqueous insoluble polymers. Amphiphilic molecules are the molecules that have hydrophobic non polar “tail” at one end and hydrophilic polar “head” to the other end.

Micelles are the colloidal suspension of the Amphiphilic molecules when Amphiphilic molecules are mixed in the aqueous medium, the nonpolar hydrophobic tails arranged inside molecules and letting the polar side.that is head to remain an outer side in direct contact with the aqueous medium and hallow spherical or cylindrical structure is formed by the process of self assembly.

Efficient down regulation of GFP gene and surviving were observed in PTX- resistant non -small cell lung cancer cell after the micely-mediated SiRNA delivery compared to free drug. In another study, prepared a PEGylated PEI-SiRNA micellar Nanoparticles that show high entrapment efficiency and long term blood circulation of SiRNA loaded Nanoparticles with reduced aggregation,opsonixation , and inflammation response.

**2.4.1.3 Carbon based nanomaterial :-**

Carbon nanomaterial (CNMs)are synthesized from allotrope of carbon such as graphene , praphene oxide (Go), nanotubes, fullerene, carbon nanotubes functionalized with PEL and pyridinium were explored for SiRNA delivery. Both functionalized cationic CNTs complexes anionic SiRNA and provide the silencing efficiency of 10-30% and 10-60% of cytotoxicity.

Recently, byutilizing the inherent properties of different newly invented CBNs. These have been modified and extensively used in biomedicine including application for bio-sensing , drug delivery and Cancer therapy. This encourage us to conduct a comprehensive review an CBNs in biochemical application.

Fullerene has a different number of carbon atoms on it's structure like C60, C70 etc . C60 is the most commonly used fullerene, having 60 cartoonists structure and is composed of 20 hexagonal rings and 12 pentagonal rings is called as Buck balls.

**2.4.1.4 Liposomes :-**

Liposomes are well ordered, self assembled vesicles of Amphiphilic lipids molecules that form a minute sperical shape Nanoparticles having single lamellar or multi- lamellar lipid bilayer structure of phospholipid molecules that have aqueous medium inside used to encapsulation and deliver drugs or genetic material into a cell . Liposomes are highly biocompatible and biodegradable, small size, vesicles of Amphiphilic lipid with the High surface are at o volume ratio.

They have some superior physicochemical properties Ike increased rate of biology membrane permeability, the flexibility of functionalization, tong of surface charge. These properties make liposomes a better Nano formulation to deliver drugs and genes than other NCs and also have been successfully applied in the clinic. Polycationic liposomes as building blocks to entrap of negatively charged SiRNA through electrostatic inter action and form lipid complexes system called Lipoplexs. So for many liposomal formulations had got the FDA approval and many more are currently in development or in clinical trials enabling features such as stable circulation and tumor specific targeting version of SiRNA liposome carries.

**2.4.1.5 Dendrimers :-**

Dendrimers are the Nano sized, sperical, monodispersed, highly branched, three dimensional, synthetic macromolecules. A typicaldendrimers molecule is composed of three structuralregions: the innermost core , comprising of atomic or molecular entity with at least two identical functional groups; branching generation with inner cavities and specific functional groups present on the surface, numerous functional groups (-COOH or -OH) are suitable for the attachment of various ligands that makes it more suitable for targeted delivery of therapeutic agents. Dendrimers are made up of repeated branching unit and form a shell of either same group and different groups, this shell is known as generation "G".

When are mixed with dendrimers know as dendriplexes. Presently, dendrimers are used for the delivery of several hydrophobic and hydrophilic drugs,genes, bio imaging agent. Depending on the type of central atom, different classes of dendrimers are available such as PAMAM (polyamidoomine), PPI (poly (propyleneimine).PLL,and poly (2,2-bis(hydroxymethyl) propionic acid etc.due to it's branch structure, several voids/spaces are formed where drugs or nucleic acids are entrapped in these voids.

**2.4.2 INORGANIC NANOCARRIERS:-**

Inorganic NCs are prepared synthetically from inorganic materials which are hard , water-insoluble,less biodegradable, toxic.Due to these limitations inorganic NCs are less used than ONCs to deliver the SiRNA molecules. Frequently used inorganic NCs are mesoporous silica nanoparticles: different metal NPs (Au NPs), selenium NPs (Se NPs), silver NPs (Ag NPs); metal oxide NPs like super- paramagnetic iron oxide Nanoparticles (SPIONS). Bara inorganic NCs are less biocompatible and have low SiRNA loading capacity than ONCs. The reason is that these NCs are mainly solid and therefore they are unable to encapsulate any molecule. The molecules can only be adsorbed of any molecules on it's outer most surface. For increasing their biocompatibility and loading capacity outer surface of these NCs are coated with several biocompatible, biodegradable, natural or synthetic polymers and lipids.

**2.4.2.1 Mesoporous silica and silica based Nanoparticles :-**

The use of mesoporous silica nanoparticles (MSNS) is increasing in biomedical and pharmacy filled. MS NPs are not only having a sperical shape, high surface area, tunable small size, biocompatibility, and biodegrade ability, easily surface functionality but also have several ordered porous structural surfaces.

Therapeutic hydrophobic drugs, bio imaging agents, genes, and chemotherapeutic agents are trapped or stored in these pores. Due to this specific character, MSNS show some advantages of high loading efficiency and controlled release of encapsulate agents. Further, MSNS are small in size with a diameter ranging between 50 and 200nm, therefore they are passively transported and across

membrane barrier and give EPR effect through and leaky vasculature and accumulate in the tumor cells. Homogeneous, monodispersed MSNS are mostly synthesized by the sol gel method. For high loading and specific site of delivery of anionic SiRNA.

MSNS are coated with cationic polymers, PEG, PEI and amine – terminated PAMAM Dendrimers

**2.4.2.2 Calcium phosphate core – shell Nanocarriers :-**

Calcium phosphate ( CaP) particles are most commonly used biodegradable inorganic carrier for high loading of SiRNA. Cap is a component that is also present in human bones. CaP particles have several demerits also they are obtained in micro – sized with polydispersed. Nano sized mono dispersed CaP NPs was obtained, when they were precipitated with PEG . CaP NPs are not show only toxicity at a higher concentration than RNAi induced concentrations and also shown better control over endogenous VEGF mRNA expression in cultured pancreatic cancer lines.

Research synthesized lipid/calcium/phosphate core shell Nanoparticles (LCP NPs) by micro emulation technology for improving systematic delivery of anti-lucifer-asaSiRNA. In this type of NPs calcium phosphate core is surrounded by cationic lipid shell and ecoratedby ananis amide ligand complementary for sigma receptor on B16F10 melanoma cell surface. After IV injection of SiRNA, the luciferase luminescence signal in metastatic B16F10 tumor cell was significantly diminished in C57BL/6 mice. Several others studies have also been done for systemic delivery of SiRNA using CaP NPs inorganic Nanoparticles.

**2.4.2.3 Metal and metal oxide Nanoparticles :-**

From the last few decades, scientist and researchers have developed, tested and applied several types of metal (gold, silver, selenium, cobalt, nickel etc).and metal oxide citron oxide, silver oxide, manganese oxide etc). NPs for the biochemical applications.

Initiy, Au NPs were used only for drug delivery, bio molecular sensing, and hyper thermal therapy. However, currently, Au NPs are also being used in intracellular gene delivery and therapy due to their unique and controlled optical properties and easy alteration of surface with thiolate molecules. Giljohann et al prepared the polyvalentSiRNA- gold nanoparticles conjugate (SiRNA-Au NPs) which was more stable in 10% serum, exhibited a prolonged half-life and more knock down of luciferase gene expression than to free RNA duplexes. The rear several ways to load a sufficient amount of SiRNA on Au NPs.

1. Thiel bond SiRNA is directly attached on Au NPs surface via a gold Thiel (R-S-H) bond.

2. Ionic bond- anionic SiRNA can be attached on the surface of the cationic Au NPs due to the electrostatic interaction.

3. Polymer coated surface – SiRNA adhered to the Au NPs surface coated with biocompatible and biodegradable with polymers.

**2.4.3 HYBRID NANOCARRIERS:-**

Organic and inorganic NCs are having their individual benefits and have been applied to remove various hurdles in delivering genetic materials. However both classes of NPs has some limitations. Inorganic NPs such as MSNs may have more stability, mechanical , chemical and imaging properties but accumulates as non degradable substance and confers toxicity. On the other side, organic NCs such as polymers, liposomes and micelles are biocompatible as well as biodegradable with high encapsulation efficiency both on the surface and within the core, but less stable in – vivo , for removing the drawback of both types of NPs, the hybrid NCs are the best solution. These hybrid NCs are prepared with the fusion of both organic and inorganic NCs. numerous biocompatible and biodegradable polymers are coated or grafted on the surface of both NCs. These polymers increase biocompatibility loading tendency of genes with reduced toxicity. Meanwhile the inorganic constituent provide diagnostic of therapeutic properties. Therefore the hybrids NCs have benefit to offers the theranostics application with high delivery efficiency.

**2.5 ADVANTAGES AND DISADVANTAGES OF NANOCARRIERS:-**

- **ADVANTAGES :-**

a) accumulation in the target cell
b) Improve bioavailability
c) Sustain release of drug
d) Protection of SiRNA against enzymatic degradation (nuclease and protease)

- **DISADVANTAGES :-**

a) Poor hydrophobicity
b) Low accumulation

**2.6 PHYSICOCHEMICAL PROPERTIES OF NANOCARRIERS:-**

a) Zeta potential
b) Surface properties
c) Particle size
d) Drug loading capacity
e) Drug release
f) Targeted drug delivery
g) Thermal stability
h) pH stability

**2.6 APPLICATION OF NANOCARRIERS IN VARIOUS TYPE OF CANCER:** Cancer occurs by either over expression of genes in to cells or by mutation of Genes. It can also occur by loss of natural cell death mechanism, which leads to uncontrolled Growth of cells. So SiRNA suppress the genes which cause cancer.

**2.6.1 Lung Cancer:-**

A cancer that being in the lungs and most often occurs in people who Smoke. Lung cancer is a type of metastasized; can spread into the whole body, which leads to treatment unsuccessful by chemotherapy drugs and radiotherapy. It can be treating by delivering the SiRNA which is carried out by nanocarriers into the tumorous. Epidermal growth factor receptor (EGFR) is seen to be over expressed in various types of cancer. Including lung cancer also. In lung cancer, EGFR mutation takes places. Most common mutation happens on exons 19. Exons 19 deletions take place, which leads to the activation of EGFR and cause uncontrolled growth. It can be treated by which target the EGFR mutants which decrease the growth of tumor by silencing the tumor associated genes. SiRNA target mutant EGFR without targeting the normal EGFR and gives safe therapy. Positively charged single-walled carbon nanotube (-CONH – (CH2)6-NH3+) were used carry SiRNA targeting telomerase reverse transcriptase into Cancer cells.

**2.6.2 Liver cancer:-**

Cancer that being in the cells of the liver. HCC (hepatocellular carcinoma is the type of liver cancer. It is not only caused by mutation of genes but also caused by virus like hepatitis viruses. HCC is majorly triggered by the hepatitis B and C infections. It is treated by the transplantation in a limited patient for whom donors are present. So this treatment is not used widely because of available of donors, so another treatment, SiRNA formulation is used, which selectively target the liver tumors and causes genes suppressing which associated in the liver cancer.

**2.6.3 Prostate Cancer:-**

It is the type of malignant Cancer which occurs in men, it is caused by mutation of genes or by androgens. It is treated by various approaches like prostatectomy, anti androgenic Harmon therapy, radio therapy, chemotherapy. But all these approaches give harmful effect on the working or normal tissue. So it can be treated by RNAi mechanism by SiRNA. Prostate cancer is greatly increased by over expression of androgen receptor, so SiRNA block the gene which causes over expression of receptor.

**2.6.4 Breast Cancer:-**

It is death causing Cancer in women breast cancer can be caused by over expression of three receptors: oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2). Oestrogen receptor are two types one is ER@ and second is ER$, mostly breast cancer is associated with ER@ and with over expression of estrogen receptor. So SiRNA inhibit the expression of receptor and decrease the risk of breast cancer.

**2.6.5 Ovarian Cancer:-**

It is a death causinggynecologic cancer in women. It is treated by the platinum- taxon medicine, but chances of reappearance of tumor are always here with the treatment of platinum– taxon. Ovarian cancer is caused by the loss of BRCA1, tumor reducing gene. So there is a need of target to treat this cancer by SiRNA

**3. RECENT FINDING:-**

As of now there is no approved as of now there is no approved therapy for.RNAi mediated treatment offers many advantages by the introduction of various SiRNA targeting the strain of EBOV into cocktail. However, to deliver the SiRNA, carrier system should be such that it delivers the SiRNA more efficiently and protects the SiRNA, cationic liposomes is choice of vehicle but it causes the

cytotoxicity at particular dose, human can tolerate the toxicity. Lipid Nanoparticles (LPN) delivers the SiRNA into the hepocytes, a major platform of replication. Recently anti- EBOV SiRNA was tested and appeared useful and non toxic to human.

## 4. FUTURE PROSPECTIVE:-

Gene blocking therapy by SiRNA through RNA is a milestone discovery. RNAi works on the degradation of messenger RNA (mRNA) to suppress the particular type of genes. Even SiRNA has great therapeutic effect, it has various disadvantages and that is why it is easily approved by FDA. So to increase the use of SiRNA as therapeutic agent, the two demerits first is off target inhibiting and second is immune stimulation, should be detached. Various reasons are responsible for off targeting effect like immunoreponse. First, it is consequences of the chemical modification, secondly, it is due to the recognition by the immune receptor like TLR (toll like receptor) as a foreign agent mainly it is because of the little homology with SiRNA other SiRNA so these all drawbacks should be detached. Now after that problem are associated with efficient reaching of SiRNA into target cell.

Virus vector has disadvantages like immunoreponse and mutagenesis. So use of viral vector is limited because of the bottleneck. So attention is paying on the non viral. Cationic polymers, lipid based delivery and Nanoparticle associated delivery is used but cationic liposome cause cytotoxicity. That is why natural liposome should be used more and attention should be given to decrease the toxicity of cationic lipid because for a new therapeutic drug, safety is very important, future development should carry on the efficient delivery vechial and nucleus resistance of SiRNA.

## 5. CONCLUSION:-

In conclusion, nanocarriers are promising delivery tool for the hormones, cytokines, nucleic acids, vaccines, antibodies, enzymes, and gene- and cell-based therapeutics for the treatment of multiple pathological conditions. Biotechnologies such as genetic engineering or hybridoma technique

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