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Review Article

An Overview Of Nucleic Acid Based Therapeutic Delivery System

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ABSTRACT

They are the novel approach which are widely used the treatment of various diseases by alteration or replacing and by the supplementation of genes or by the the treatment of diseases which are caused by the absence or abnormal genes. In this there is insertion of foreign genes into the organisms for the treatment of defective gene which are responsible for causing abnormal diseases. In this approach we use the DNA or RNA so we can modify and rectify the defective genes. This system use several methods for treating various diseases like RNA interference (RNAi), gene therapy, Antisense Oligonucleotide techniques. In this most widely used method is Gene therapy which are used in the treatment of various diseases by using the gene information which are transfred for the phenotypic changes which give effective treatment.

INTRODUCTION

In this novel approaches, on the basis of magic bullet that method is used to transfer the the therapeutic agents to the targeted sites in the body for the treatment of several diseases[1]. These drug delivery system are able to changes the biological and physicochemical properties of drugs which may cause dissimilarities in biodistribution and pharmacolkinetic of cargo[2]. In this delivery system the gene therapy are available which are used for the maintainence of non-coding and coding of genes which are mean to be targeted and providing therapeutics propperties for a several diseases like cancer, transmission diseases and genetic diseases. The industries of pharmaceutical and biotechnology produces large variety of drugs based on nucleic acid. In a current scenario, the nucleic acid based drugs have been certified for commercial use allowed from the US Food Drug And Safety (FDA) many oligonucleotides and RNA interfernce (RNAi) drugs are come under clinical trials of Phase- III which comprise of ALN-TTR02 (Alnylam Pharmaceuticals), QPI-1002 (Quark Pharmaceuticals) and alicaforsen (Atlantic Healthcare)[3]. Nucleic acid based drug delivery system developing a most effective and

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safe delivery of gene in-vivo and has now become the most important objective for the medical prospect of gene therapy[4]. In this there are some drawback because in the some previous year these delivery system was made nucleic based drugs which was used for the therapeutic use in some diseases which was found from the liver[5] and in tissues also by directly injecting drugs in specific areas like eyes and spinal cord[6]. In translational scientific investigation, the little particles and recombinant proteins have been the play a important roles and driving the medical progress. These little particles provides advantages like ability to penetrate cells and lack of immune response and articially tuned to interact with the specific proteins[7].

GENE THERAPY:

The gene therapy is a insertion of new genetic material to the human brain to produce a desired therapeutic effects[8]. This gene therapies are used to treat several diseases through replacement of deffective with the healthy genes. Now in a current scenario deoxyribonucleic acid (DNA) are used as a medicine which decreases the symptoms of diseases but this therapy is not always corrective in tradiotional sense of response of body changes. In other words the gene therapy are providing the chances for the treatments of the conditions which were once considered deffected and providing hopes for the better health of children and adult patients[9]. Mostly in the gene therapies clinical studies it is observed that therapy target the somatic cells which are alive as stays as patient live so this clear that the gene therapy will affect the patient receieving it and will not cause the alteration in the genetic make up of the offsprings this means this effective gene is not transfer in the gametes so it is called a Somatic gene therapy. More than 300 clinical studies it found that therapeutic is transferred to the patients which certified and represent the success in the treatment by gene therapy, USFDA are approving the first nucliec acid drug is Formivier which are available in the market as a trade name Vietravene which are used in the treatment of viral retinitis patients[10]. When the therapeutic genes is transferred to germ cell line at premature stage of embryo growth this is called Germ line gene therapy, this is tranfered to future generation that is the reason are not used in this current scenario[11].

TYPES OF GENE THERAPY:

There are several types of somatic cell of gene therapy are-

1. **Ex vivo delivery:**

In the Ex-vivo gene delivery, the genes are removed from the tisses and bone marrow which are targeted and then cultered and then controlled invitro and then transferred to targeted tissues and in this no immune complication are involved and this is only used when the target is the vaccine or secreted protein. This method also used as therapeutic treatment for the cancer and very few reintroduced cells are alive[12].

2. **In situ delivery:**

In this type of delivery direct delivery of the genes to the specific desired tissues. In this CTFR gene is transferred through the adinoviral vectorIn and lipids to the repiratory regions which allow the therapeutic actions against the cancer. In this system mutation is the drawback of the system because the malignant cell can reproduce the tumor[13].

3. **In vivo delivery:**

In this type of delivery the genes are passed through the both type of vector (viral or non-viral vectors) to specfic tissues is called In vivo delivery. The major drawback is not proper transfer of genes to the specific desired tissues[14].

APPLICATIONS OF VECTORS IN GENE THERAPY:

1. **Viral vectors:**

They are the most adequate vectors which are known for the transfer the genes because they can infect many cells. Bacteria are the best vectors for

transmit of transgenes, they can perform the natural mechanisms to deliver genes to the cells[15]. They have a virus which are modiefied which do not have the ability to preform a replication but they can abel to transfer the genes to the tissues or cells. In this there are the drawback is that due to this modified virus can cause immune reaction which lead to the damge of tissues and there are a problem of release toxins and there are also chances of occurance of mutagenesis[16].

2. Retroviruses:

These are the vectors which use Ribonucleic Acid (RNA) as a gene (genetic material). Firstly the phenomena of replication occur in which conversion of RNA into DNA then they enter the human cell genome. They contain capsid which is around the genes and envelope protein which is embedded in a lipid bilayer. Moloney murine leukemia virus (MoMuLV) are known for Gene therapy application for the therapeutic activities in Adenosine Deaminase Severe Combined Immuno Deficiency(ADA-SCID)[17].

3. Adenovirus Vectors:.

These type virus have been derived from over 100 serotypes in several species and become applicable in gene therapies. Type 2 and 5 are known for the transmission of genes to the non-dividing and dividing cells. With ground level host compatibilities, they have a capacity to transmit genes to several range of tissues[18].

4. Baculovirus:

In the famiy of baculovirdae which comprise of virus which cause infection of arthopods in the larval stage in which they infects Lepidoptera, Diptera, Hymenoptera, Coleoptera, Orthoptera, Neuroptera, Trichoptera and Thysaneura[19]. In this the Nuclear Polyhedrosis Virus (NPV) which come under the family of Baculovirdae, which is a huge circular double strandard DNA virus with a genome of 80-150kbp and more than 100 genes[20]. They are known for staple in gene expression studies for over three decades, reowned for its capacity to produce to large amount of proteins in the cells of insects. As time passes the on the basis of success of baculovirus research shows the recombinant baculovirus can abel to come inside many mammalian cells and abe to express foreign genetic materials which are in the controlled by the mammalian promoters due to no occurance of viral replications[21] this lead the reason to be used for the transfer of genetic material to mammalian cells. This is due to beneficial properties of baculovirus gene expression system are able to modify genetics and they can produce the recombinant viruses in uncomplicated way using bacmid bacteria[22] and they use eukaryotic system for post transitional modifications like glycosylation and especially in cells of mammals, they have a replication deffective properties due to no primary antibodies and very less cytotoxic as correlation with vectors which are obtain from mammalian virus. For obtaining a better genetic materials they produce they appear to trigger the immune response in the cells of mammals[23] and defend against infection of virus[24] and metasiasis of tumor which occur in mice[25].

5. Lentiviral system:

They belong to the class of retrovirus which abel to cause a chronic and severe diseases and they typically joined with the infection of distict cell type of macrophages. Researcher develop a gene transfer vector which are obtain by the lentiviruses to improves on existing retroviral vectors. These type of vectors combine this genetic materials to the host cells of DNA, don't trasmit viral genes and avoid immune rejection. They infected the non-dividing cells and spreading their usefulness in gene therapy[26].

ADVANTAGES OF GENE THERAPY:

1. They provided a proper treatments but not a end of life care or curative treatment.

2. It is that comes under the therapeutic treatment that express the several genetic disorder.
3. They protect from the transfer of disorder of genetic material and keep away from the repeated somatic cell therapy across the generations and decrease the risk and cost.
4. It is very important for the drugs to expresses the sexual fitness concern of parent facing the risk of passing on severe genetic disorder.
5. The Scientific committee should do the scientific investigation on germ line therapy within a ethical boundaries.

DISADVANTAGES OF GENE THERAPY:

1. This therapy demands a more times on clinical research and studies on the effects which expected to take a more time in the future which are not known.
2. This therapy potentially try to manipulate non-disease related human traits aggravate racial distinguish.
3. This gene therapy should do examining on very beginning developing of baby shortly after fertilization and affecting offsprings, this therapy cause raising ethical concerns.
4. This therapy is high cost may hinder it's social priortization and prevent acessibility.
5. This germ line therapy can breach the right of future genertation to inherits genetic traits that haven't been intentially altered[27].

LIPOSOME GENE DELIVERY SYSTEM:

They are essentially a spherical structures which are made up of lipids in which itself gather to form a membrane of bilayered.This membrane form a single layer and multiple layer creating a concentric vesicles. This vesicles around a water based compartmenr at their core[28]. On the basis of drug carrier the liopsome show a good activities like preventing the drugs which are encapsulated from the damage in the body[29], they just increases the drug's half life and release of drug also controlled[30], they show the good biocompatibility and show no harm to use. They release the drugs to the targeted region either by active or by passive targeting process and decreases the side effects, the maximizes the dose and enhance the quality treatments[31]. Charged Liposomes: As the growth of charged liposomes shows the beneficial features than the different types[32]. Many techniques involve the application of phospholipids which are in a charge form[33]. Liposomes are coated with chitosan[34]. After that put some stearyl amine which is a charge inducer agent which cause changes on the surace of liposome which are in the form of charged[35]. The charge liposome are of several types such as Cationic and Anioinic liposome.

Cationic liposome:

They are the type which was poineered by Felgner et al was about in 1987, possess a two advantages which are non-immunogenic and straightforward to produce[36]. They are used as for transfering several DNA, RNA and Oligonucleotides which are in negative charge and they are useful in transfer the therapeutic genetic material and vaccine inside the cells[37]. DOTMA (N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium) and DOTAP (N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium) are well for the formation of cationic liposomes[38].

Anionic Liposome:

These type of liposomes shows rapid clearance rates as comparison to cationic and neutral liposomes[39].After the opsonization to the counterpart and plasma protein they react with biological organisms[40].

ANTISENSE THERAPY:

Recently there are various disorder can be effectively treated by Antisense Oligonucleotides[41]. These were founded more than 40 years ago which led to establishment of modified proteomics and genomic tools[42]. Antisense Oligonucleotides are distinguish themselves from the conventional drugs by

targeting the mRNA and cause alteration in protein expression by various unique mechanism of actions[43]. These are involved in scientific investigation for acdequate therapeutic activities against disorder cases of several patients[44].

MECHANISM OF ACTIONS OF ANTISENSE THERAPY:

They are crafted to necessary genetic integration to bind to particular genetic sequences which are found in the specific sequence mRNA and affect the formation of abnormal proteins that is why the inactivated protein can be blocked and the root cause of disorder can be eliminated. So that in the extension scientific research confirms that the role of synthetic Antisense Oligonucleotides can act by cutting mRNA strands and blocking their functions[45].

APPLICATIONS OF ANTISENSE THERAPY:

1. **Tubulointerstitial Injury:**

In this the scientist discover that at the time they blocked te midkine gene found in mice it decreases the movement of cells which inflalated to the kidney's of tubulointerstitium after ischemia and reperfusion injury. They achieved in this by inject synthetic molecules called midkine antisense phosphorothioate oligonucleotides into the mice bloods either before or after the injury. After this scientific research it is found that using the midkine antisense therapeutics properties could be new techniques for adequate therapy for acute tubulointerstitial injury which cause due to ischemia and reperfusion damage[46].

2. **Cardiovascular diseases:**

In this conditions, some scientific investigations shows the using the oligodeoxynucleotides can decreases the appearance of ICAM-1 which are the surface adhesion molecules in reperfusion injury models. This concluded that uses the antisense therapeutic methods to target the acute renal failure and injury of reperfusions could be adequate treatment. There are some cells that release Angiotenin II molecules that can send feed back effect to those cells which are responsible for causing growth and other alterations[47].

3. **Antisens Antivirals:**

Due to the presence of some antibiotics do not give the adeaquate effects against some strain of viruses because they form the drug ressistance that cause serious illness and cause death worldwide. These viruses are Herpes viruses, Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV). The previously available drugs does not give the adquate therapeutic effects in these type of viruses, the only way treatment by giving gene silencer which is a single stranded oligonucleotides which give us a rapid respond after the treatment of viruses[48].

4. **Hepatitis B:**

The scientist develop special type of single-stranded ASO called locked nucleic acid ASO. They are designed it to target a specific site on the liver's asialoglycoprotein receptor and decreases contact with the kidneys. By associate with three N-acetylgalactosamine moieties, they conjugate with the liver cell surfaces. On the basis of scientific research in animals it reveals that the modified ASO are potent than the version without the N-acetylgalactosamine conjugation[49].

5. **Diabetes:**

For the years the old treatment like photocoagulation and vitrectomy is the way for the treatment of diabetic retinopathy. Now in the current scenario the Secondary ASO are used for the better therapeutic activity against diabetic retinopathy, this decreases the likelihood of different growth factors which includes the abnormal blood vessels growth and macular edema, a hall mark of diabetic retinopathy[50].

6. **Batten Diseases:**

In the year of 2009, the FDA issued the Clinical Investigation Report recommend the establishment of ASO drug which is Milasen that

are used for the adequate treatment of Batten diseases. The Milasen drugs was specifically tailored for targeting the mutation which are found in the single patient, for the formation of personalized therapeutic activity but it is not suitable for the patient of Batten diseases. This drawback become the case personalized drugs[51].

7. Spinal Muscular Atrophy:

SMA occur when SMN1 gene does not work which lead to no SMN protein. The Nusinersen which is a drug that fixes this by targeting SMN2 gene. They inhibiting the part called splicing silencer allow exon 7 inclusion. The FDA certified it and they are safe for use to the patient suffering from SMA[52].

8. Huntington's Diseases:

This is the common neurodegenerative condition occur due to long repeatition of CAG in the gene of huntingtin. This lead to the formation of harmful protein with the long polyglutamine tract. The Antisense oligonucleotides are designed to decrease the HTT levels and appear to long term success in Huntingto's diseases with drugs which are still on research[53].

APTAMER:

The Aptamer are the short RNA or DNA oligonucleotides that can bind to specific targets due to their special 3D shape. They were form separately by Gold and Szostak's team in 1990[54]. They are formed by the invitro method are called Systematic Evolution of Ligands by Exponential Enrichment (SELEX). This process selectively isolates aptamers that bind to precise target by repeatedly cycling through selection and amplification several times[55]. SELEX are used to amplify oligonucleotides that strongly conjugate to precise target molecules. They are establishes by three main steps which are repeated in this cycle are-

1. Oligonucleotide with respective library which are conjugated to precise targets.
2. The oligonucleotide which are not bound are removed.
3. The oligonucleotide which are attached then undergoes replication process through the application of PCR which employed the shared 3/ and 5/ which are the flanking sequence. After enhanced, libraries demonstrated adequate outcomes are choosed and these sequences are formed in enough amount to do operational aspect of aptamer performance[56].

CHALLENGES OF APTAMERS:

1. Renal Filtration:

If the Aptamer mass are about 6-30kDa and they has a normally diameter which is below 5nm. The Aptamer which are not in formulated form and they are supplied to the blood and in this the aptamer which are given undergo stabled due to their certain alteration in their structure of backbone but even after all of this they are excreated by a renal filtration due to small size this lead to decrease in time of circulation. To decrease this challenges they undergoes to certain altration by joining large molecules such as protein, cholesterol, liposomes, organic and inorganic nanosubstances or by clustered together to increase mass above the threshold that kidney filtration system allow about 30-50kDa[57].

2. Toxicity:

When assesing drug factors like toxicity, side-effects and immunogenicity are the important parameter along with efficacy and shelf life. They provide benefits on antibodies because of low or no antibodies properties. Initial preclinical research, Pegaptanib sodium also known as Macugen and they are basically a aptamer drug which are made to protect from wet age-related macular degeneration and did not show any systematic effects in preclnical research[58].

3. Automization of SELEX protocols:

In choosing a Aptamer are a repeatable and long time taking and labor intense action. In PCR

amplification procedure for enhancing of choosed aptamer in which many times PCR process occur that cause operator error. Advancement in molecular biology have seen automation in various function like plasmid formation, sequencing of DNA and microassay design[59]. The automation of aptamer selection procedure decreases differences that result in decrease repeatability of outcomes. According to the circumstances of automation accomplished, there will be decrease in labor, material, supplies and time while production are enhanced by parallelization. The degree of test automation depends on the time, duration and revenue distribution of the project[60].

APPLICATIONS OF APTAMER:

1. **Prophylaxis:**

They are versatile molecule with the utilization above the drug targeting. In this preventive measure way, the aptamers play a vital role in conjugated to a specific molecule[61]. Whether they are extracellular, intracelluar and ATP. In a current scenario, the risk of uninary tract infection enhanced[62].

2. **Biosensor:**

The Biosensor Aptamerscan are widely applied for the determination of pollutant of environment. By the utilization in the chip based biosensor array where they are immobilize on a glass-slide and labelled with the mark of fluoroscent[63].

3. **Research Tools:**

They are mostly used in the research purpose. They are obstructing the intracellular signaling pathway. The one prominent representative inhibitory aptamer such as Mitogen Activated Protein Kinase (MAPK) RNA aptamers[64].

4. **Molecular Mimics:**

The Aptamer are choosen through straight forward process called SELEX which increase the efficiency of Aptamers. The complex RNA are engineered and choosen for the precise functionalties. An illustrative representative of aptamer which act like a molecular mimics is the Spinach aptamer which comes under RNA and to stimulate green fluroscent protein[65].

CONCLUSIONS:

In a current scenario this delivery system are now become the most widely used approaches for the treatment of several genetically based diseases through the gene therapy, they are used because of unique and versatile properties than the other delivery system. This system basically offers the targeted therapies to deliver the gene to the targeted region to give the adequate effects without causing the adverse and side effects in the body. There are several way are available in this delivery system are Aptamer, siRNA, Antisense Oligonucleotide are made to target the several disease pathway. The nucleic acid based drug delivery system face the barriers like the responses of immune and problems in deliveries. The scientist working in this problem to decreases these difficulties. There main objective to achieve the safety and great efficacy in this therapeutic treatments. In the Antisense therapies shows adequate treatment by giving targeted therapies to the several disorder. Using the antisense oliginucleotide that choose the RNA squencing and regulate the expression of genetic materials and suppress the defective protein and that lead to decrease the apperance of the diseases. On the basis of Aptamer they are also contain oligonucleotides and peptides and they are also target the precise molecule and giving the adequate therapeutics effects. They are use in the diagnosis and treatment purpose to the patients that suffered from several disorder. As going in this generation there are a modication in aptamer they are giving more precise treatment to the patients and they are also used as a precised drugs to the specific patients and giving the better results.

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