ABSTRACT

Novel treatment modalities like gene therapy and cell therapy are attractive for such diseases where current therapies have failed. Although the clinical potential of these therapies has been demonstrated in the West, their use still remains in experimental stages. In India a number of groups are carrying out basic research on gene delivery vector development and strategies for cancer gene therapy, and development of adult and embryonic stem cells. With the establishment of human embryonic stem cell (hESC) lines in a few centres, India is now geared to become one of the major contributors to the emerging field of DSC. This review will cover some of the published and unpublished work with potential to be translated into clinical trials, and discuss the possible hurdles in carrying out clinical trials. Much attention has been focused on the so-called genetic metabolic diseases in which a defective gene causes an enzyme to be either absent or ineffective in catalyzing a particular metabolic reaction effectively.

Keywords: Clinical trials, gene and cell therapy, human embryonic stem cells, viral vectors.

1. Introduction

Gene therapy is the introduction of genetic material into cells for therapeutic purposes. Recent scientific breakthroughs in the genomics field and our understanding of the important role of genes in disease has made gene therapy one of the most rapidly advancing fields of biotechnology with great promise for treating inherited and acquired diseases. As gene therapy has moved from the laboratory into the clinic, several issues have emerged as central to the development of this technology: gene identification, gene expression and gene delivery. Gene identification was originally tackled by academic researchers supported by the government's Human Genome Project and more recently through genomics companies. Genes with broader clinical application are also being utilized to make cells express immune activating agents locally at the disease site or to become susceptible to further drug treatment or to immune response recognition [18]. Genes, which are carried on chromosomes, are the basic physical and functional units of heredity. Genes are specific sequences of bases that encode instructions on how to make proteins. Although genes get a lot of attention, it’s the proteins that perform most life functions and even make up the majority of cellular structures. When genes are altered so that the encoded proteins are unable to carry out their normal functions, genetic disorders can result [26].

A potential approach to the treatment of genetic disorders in man is gene therapy. This is a technique whereby the absent or faulty gene is replaced by a working gene, so that the body can make the correct enzyme or protein and consequently eliminate the root cause of the disease. The Human Genome Program in the U.S. will provide about $200 million each year to scientists in multidisciplinary research centers who are attempting to determine the makeup of all human genes. Together with similar programs in Europe, it is hoped that in 15 years’ time we shall be able to identify and treat all diseases to which humans are susceptible. This will revolutionize modern medicine, and hopefully improve the quality of life of all men, women, and children. Already, the genes for Duchene muscular dystrophy, cystic fibrosis, and retinoblastoma have been identified, and more such information is emerging all the time [1].
1.1 Considerations
Gene therapy is ‘the use of genes as medicine’ involving the transfer of a therapeutic or working copy of a gene into specific cells of an individual in order to repair a faulty gene copy.\[2\]

1. The technique may be used to replace a faulty gene, or to introduce a new gene whose function is to cure or to favorably modify the clinical course of a condition.
2. Gene therapy is still an experimental discipline and much research remains to be done before this approach to the treatment of condition will realize its full potential.
3. The challenge of developing successful gene therapy for any specific condition is considerable:
   - The condition in question must be well understood
   - The underlying faulty gene must be identified and a working copy of the gene involved must be available
   - The specific cells in the body requiring treatment must be identified and accessible
   - A means of efficiently delivering working copies of the gene to these cells must be available
4. The problem of ‘gene delivery’ i.e. how to get the new or replacement genes into the desired tissues, is very complex and challenging.
5. Some of the ‘vectors’ for the role of delivering the working copy of the gene to the target cells include using harmless viruses and stem cells.
6. In gene therapy, only body (somatic) cells and not the egg or sperm cells (germ cells) are targeted for treatment.
7. Somatic gene therapy treats the individual and has no impact on future generations as changes to the somatic cells cannot be inherited.
8. The strong consensus view at present is that the risks of manipulation of the genes in the egg or sperm cells far exceed any potential benefit and should not be attempted.\[3\]

1.2 Types of Gene Therapy: Gene therapy may be classified into the two following types: \[4-8\]

1.2.1 Germ line gene therapy
In the case of germ line gene therapy, germ cells, i.e., sperm or eggs, are modified by the introduction of functional genes, which are integrated into their genomes. Germ line gene therapy involves making changes to the cells that are used in the reproductive process. Germ line gene manipulation can change sperm cells, oval or stem cells precursors. In order for germ line therapy to produce changes that will be transmitted to offspring, the genes need to be inserted into chromosomes. Germ line therapy has so far mainly been used in animals. Germ line gene therapy involves the genetic modification of germ cells (sperms and eggs) in order to prevent a genetic defect from being transmitted to future generations. Here gene therapy is applied to somatic cell of the host and thus the altered gene is restricted to the individual only, and not passed down the generations. This method is considered safer for humans.\[6-8\] However, many jurisdictions prohibit this for application in human beings, at least for the present, for a variety of technical and ethical reasons.\[9\] This new approach, theoretically, should be highly effective in counteracting genetic disorders.

1.2.2 Somatic gene therapy
In the case of somatic gene therapy, the therapeutic genes are transferred into the somatic cells of a patient. Expression of the introduced gene relieves symptoms of the disorder, but this effect is not heritable, as it does not involve the germ line. It is the only feasible option, and clinical trials have already started mostly for the treatment of cancer and blood disorders.\[10, 11\] Somatic gene therapy treats somatic cells by inserting an agent containing a modified gene (known as a vector) into a person's body. Somatic cells are cells that form the body and cannot produce offspring. Gene therapy, in its present stage, only treats somatic cells in humans. There are two types of somatic gene therapy, ex vivo and in vivo. Ex vivo modifies cells outside the body and then transplants them back into the body. In vivo changes the cells while they are still in the body; Somatic gene therapy does not affect any offspring of the person being treated.\[12\]

1.3 Advantage & Disadvantage of gene therapy

1.3.1 Advantage
- The advantage of the technique is to give someone that is born with a genetic disease or who develops cancer the chance at a normal life.
- I think this is an advantage that far outweighs any of the disadvantages that have been presented against gene therapy.
- Giving someone a chance at a normal life should be enough for many of the people that oppose this technique to change their minds.
- Effective
- Stable and long-term expression of the protein (up to a year with lentiviral vectors)\[13\].
- Localised to the injection site
- Possibility of targeting specific cell populations (with aid of cell-type specific promoters or modifying viral coat proteins)\[4\].
- Continuous supply of the protein of choice (as opposed to injecting bolus injections at specified intervals).\[13\]

1.3.2 Disadvantage
- The basis of gene therapy is find a gene that is not functioning right and to insert a healthy portion into that gene.
- To find these genes, scientists must perform genetic tests or genetic screening to the gene that causes for example, cystic fibrosis, is present.
- This genetic testing is producing much controversy and raising many ethical and legal problems.
- Many believe that this is an invasion of privacy. They believe that if prenatal tests are performed that these could lead to an increase in the number of abortions.
- Pathogenicity (although most vectors are engineered to have the pathogenesis inducing sequences removed)\[14\].
- Immune response (mostly a problem with AdV and HSV vectors). Research currently underway to construct new
generation vectors devoid of immune reactions.\textsuperscript{[13]}  
- Incorporation into the host genome may lead to derepression of tumour suppression genes.\textsuperscript{[13]}  
- Difficult to control the exact amount of viral product and the duration of expression (may be possible to bypass this using encapsulated ex-vivo genetically modified cells or self-inactivating cassettes\textsuperscript{[13]}

1.4 Vector used in Gene Therapy
Vector a molecule, particle, organism, or other carrier that transports molecules such as genes to a recipient.\textsuperscript{[4, 10, 13]} The various carrier molecule for gene therapy were include:

1.4.1 Retroviruses: - The genetic material in retroviruses is in the form of RNA molecules. When a retrovirus infects a host cell, it will introduce its RNA together with some enzymes, namely reverse transcriptase and integrase, into the cell. This RNA molecule from the retrovirus must produce a DNA copy from its RNA molecule before it can be integrated into the genetic material of the host cell. The process of producing a DNA copy from an RNA molecule is termed reverse transcription. It is carried out by one of the enzymes carried in the virus, called reverse transcriptase. After this DNA copy is produced and is free in the nucleus of the host cell, it must be incorporated into the genome of the host cell. That is, it must be inserted into the large DNA molecules in the cell (the chromosomes). This process is done by another enzyme carried in the virus called integrase. Now that the genetic material of the virus has been inserted, it can be said that the host cell has been modified to contain new genes. If this host cell divides later, its descendants will all contain the new genes. Sometimes the genes of the retrovirus do not express their information immediately. Gene therapy trials to treat SCID due to deficiency of the Adenosine Deaminase (ADA) enzyme continue with relative success in the USA, Britain, Italy and Japan.

1.4.2 Adenoviruses
Adenoviruses are viruses that carry their genetic material in the form of double-stranded DNA. They cause respiratory, intestinal, and eye infections in humans (especially the common cold). When these viruses infect a host cell, they introduce their DNA molecule into the host. The genetic material of the adenoviruses is not incorporated (transient) into the host cell's genetic material. The DNA molecule is left free in the nucleus of the host cell, and the instructions in this extra DNA molecule are transcribed just like any other gene. The only difference is that these extra genes are not replicated when the cell is about to undergo cell division so the descendants of that cell will not have the extra gene. As a result, treatment with the adenovirus will require re-administration in a growing cell population although the absence of integration into the host cell's genome should prevent the type of cancer seen in the SCID trials. This vector system has been promoted for treating cancer and indeed the first gene therapy product to be licensed to treat cancer, Gendicine, is an adenovirus. Gendicine, an adenoviral p53-based gene therapy was approved by the Chinese FDA in 2003 for treatment of head and neck cancer.

1.4.3 Adeno-associated viruses (AAV)
Adeno-associated viruses, from the parvovirus family, are small viruses with a genome of single stranded DNA. The wild type AAV can insert genetic material at a specific site on chromosome 19 with near 100% certainty. But the recombinant AAV, which does not contain any viral genes and only the therapeutic gene, does not integrate into the genome. Instead the recombinant viral genome fuses at its ends via the ITR (inverted terminal repeats) recombination to form circular, episomal forms which are predicted to be the primary cause of the long term gene expression. In contrast to adenoviruses, most people treated with AAV will not build an immune response to remove the virus and the cells that have been successfully treated with it. Several trials with AAV are on-going or in preparation, mainly trying to treat muscle and eye diseases; the two tissues where the virus seems particularly useful. However, clinical trials have also been initiated where AAV vectors are used to deliver genes to the brain. This is possible because AAV viruses can infect non-dividing (quiescent) cells, such as neurons in which their genomes are expressed for a long time.

1.4.4 Envelope protein pseudo typing of viral vectors
Retroviruses have limited natural host cell ranges, and although adenovirus and adeno-associated virus are able to infect a relatively broader range of cells efficiently. Attachment to and entry into a susceptible cell is mediated by the protein envelope on the surface of a virus. Retroviruses and adeno-associated viruses have a single protein coating their membrane, while adenoviruses are coated with both an envelope protein and fibers that extend away from the surface of the virus. The envelope proteins on each of these viruses bind to cell-surface molecules such as heparin sulfate, which localizes them upon the surface of the potential host, as well as with the specific protein receptor that either induces entry-promoting structural changes in the viral protein, or localizes the virus in endosomes where in acidification of the lumen induces this refolding of the viral coat. In either case, entry into potential host cells requires a favorable interaction between a protein on the surface of the virus and a protein on the surface of the cell. Most attempts to limit tropism have used chimeric envelope proteins bearing antibody fragments. These vectors show great promise for the development of "magic bullet" gene therapies.

1.4.5 Replication Vectors
A replication-competent vector is used in replicating tumor cells. ONYX-015 is replication-competent. An example of this is ONYX-015. It was found in the absence of the E1B-55Kd protein, adenovirus caused very rapid apoptosis of infected, 53(+) cells, and this results in dramatically reduced virus progeny and no subsequent spread. Apoptosis was mainly the result of the ability of EIA to inactivate p300. In p53(-) cells, deletion of E1B 55Kd has no consequence in terms of apoptosis, and viral replication is similar to that of wild-type virus, resulting in massive killing of cells. A replication-defective vector deletes some essential genes. These deleted genes are still necessary in the body so they are replaced with either a helper virus or a DNA molecule.

1.4.6 Cis and trans-acting elements
Replication-defective vectors always contain a “transfer construct”. The transfer construct carries the gene to be transduced or “transgene”. The transfer construct also carries the sequences which are necessary for the general functioning of the viral genome: packaging sequence, repeats for replication and, when
needed, priming of reverse transcription. These are denominated cis-acting elements, because they need to be on the same piece of DNA as the viral genome and the gene of interest. Trans-acting elements are viral elements, which can be encoded on a different DNA molecule. For example, the viral structural proteins can be expressed from a different genetic element than the viral genome.

1.4.7 Herpes Simplex Virus
Herpes Simplex Virus is a human neurotropic virus. This is mostly examined for gene transfer in the nervous system. The wild type HSV-1 virus is able to infect neuron. Infected neurons are not rejected by the immune system. Though the latent virus is not transcriptionally apparent, it does possess neurone specific promoters that can continue to function normally. Antibodies to HSV-1 are common in humans, however complications due to herpes infection are somewhat rare.

1.4.8 Oligonucleotides
The use of synthetic oligonucleotides in gene therapy is to inactivate the genes involved in the disease process. There are several methods by which this is achieved. One strategy uses antisense specific to the target gene to disrupt the transcription of the faulty gene. Another uses small molecules of RNA called siRNA to signal the cell to cleave specific unique sequences in the mRNA transcript of the faulty gene, disrupting translation of the faulty mRNA, and therefore expression of the gene. A further strategy uses double stranded oligodeoxynucleotides as a decoy for the transcription factors that are required to activate the transcription of the target gene. The transcription factors bind to the decoys instead of the promoter of the faulty gene, which reduces the transcription of the target gene, lowering expression. Additionally, single stranded DNA oligonucleotides have been used to direct a single base change within a mutant gene. The oligonucleotide is designed to anneal with complementarity to the target gene with the exception of a central base, the target base, which serves as the template base for repair. This technique is referred to as oligonucleotide mediated gene repair, targeted gene repair, or targeted nucleotide alteration.

1.4.9 Lipoplexes and polyplexes
To improve the delivery of the new DNA into the cell, the DNA must be protected from damage and its entry into the cell must be facilitated. To these end new molecules, lipoplexes and polyplexes, have been created that have the ability to protect the DNA from undesirable degradation during the transfection process. Plasmid DNA can be covered with lipids in an organized structure like a micelle or a liposome. When the organized structure is complexed with DNA it is called a lipoplex. There are three types of lipids, anionic (negatively charged), neutral, or cationic (positively charged). Initially, anionic and neutral lipids were used for the construction of lipoplexes for synthetic vectors. However, in spite of the facts that there is little toxicity associated with them, that they are compatible with body fluids and that there was a possibility of adapting them to be tissue specific; they are complicated and time consuming to produce so attention was turned to the cationic versions. The most common use of lipoplexes has been in gene transfer into cancer cells, where the supplied genes have activated tumor suppressor control genes in the cell and decrease the activity of oncogenes. Recent studies have shown lipoplexes to be useful in transfecting respiratory epithelial cells, so they may be used for treatment of genetic respiratory diseases such as cystic fibrosis. Complexes of polymers with DNA are called polyplexes.

1.4.10 Dendrimers
A dendrimer is a highly branched macromolecule with a spherical shape. The surface of the particle may be functionalized in many ways and many of the properties of the resulting construct are determined by its surface. In particular it is possible to construct a cationic dendrimer, i.e. one with a positive surface charge. When in the presence of genetic material such as DNA or RNA, charge complementarity leads to a temporary association of the nucleic acid with the cationic dendrimer. On reaching its destination the dendrimer-nucleic acid complex is then taken into the cell via endocytosis.

1.5 Disease of Genetic Disorder
Most of us do not suffer any harmful effects from our defective genes because we carry two copies of nearly all genes, one derived from our mother and the other from our father. The only exceptions to this rule are the genes found on the male sex chromosomes. Males have one X and one Y chromosome, the former from the mother and the latter from the father, so each cell has only one copy of the genes on these chromosomes. In the majority of cases, one normal gene is sufficient to avoid all the symptoms of disease. If the potentially harmful gene is recessive, then its normal counterpart will carry out all the tasks assigned to both. Only if we inherit from our parents two copies of the same recessive gene will a disease develop. On the other hand, if the gene is dominant, it alone can produce the disease, even if its counterpart is normal. Clearly only the children of a parent with the disease can be affected, and then on average only half the children will be affected. [28]

1.5.1. Genetic Disorder in Humans:
There are thousands of genetic disorders in humans. Some are common whereas quite a few are rare. Whatever be their incidence, what is most vexing about these disorders is that scientists are still trying to find cures for these disorders. While some headway has been made in the direction, a lot more research is required. Here is a comprehensive view of genetics and various genetic disorders in humans.

Fig 1: Human Chromosome Structure

Within their coiled strands, chromosomes hide a world of information about how a person should look, how tall he should be, what should be his skin color and also the diseases that he may be
prone to (which are referred to as genetic disorders in human). They have this information coded in the form of nucleotide sequences that form DNA (deoxyribonucleic acid) molecules. A single molecule of DNA is coiled to form a single chromosome. These chromosomes are present in pairs. Human beings have 23 pairs of chromosomes or 46 chromosomes in all. Of them, 1 pair forms the sex chromosomes. The rest 22 pairs are the autosomes. Sex chromosomes are of two types - X and Y. A man has one X and one Y chromosome (XY) while a woman has two X chromosomes (XX). It is just the difference of one sex chromosomes that decides individual’s gender. The chemical information of every organism is specifically coded in the nucleotide sequences of genes - the unit of heredity. Each gene codes for an enzyme that plays an important role in various biochemical reactions. In other words, a gene contains a specific sequence of nucleotide bases that are responsible for the organization of amino acids in the correct order to form an enzyme. Any disruption in this sequence causes genetic disorders in humans. Now you can understand the importance of genetics and the reason why so much of research is being done in the field of human genetics. Understanding genes will not only help us unravel the chemical blueprint of human beings, it will also enable us to deal with genetic disorders in humans for most of which, till date, there is no cure.

1.5.2. Causes of Genetic Disorder in Humans:
Genetic diseases in humans are caused due to abnormalities in genes or chromosomes. [16, 17] Such defects can be caused by the following mechanisms:

A. Mutations: These are sudden inheritable changes in the nucleotide sequence of a gene.

B. Aneuploidy: Aneuploidy is caused when there are abnormal numbers of chromosomes in an organism. This could be due to loss of a chromosome (monosomy) or presence of extra copy of a chromosome (trisomy, tetrasomy, etc.)

C. Deletions: Loss of a part of chromosome as in the case of Jacobsen syndrome.

D. Duplications: Duplication of a portion of chromosome that results in extra amount of genetic material.

E. Inversions: Inversion of the nucleotide sequence because a portion of chromosome has broken off, got inverted and reattached at the original location of the chromosome.

F. Translocations: When a portion of chromosome has got transferred on to some other chromosome. Sometimes translocation can take place between two chromosomes, in which case they interchange chromosome segments. However, in some cases a portion of a chromosome may simply get attached to another chromosome.

1.5.3 Types of Genetic Disorder in Humans:

A. Autosomal Dominant Genetic Disorder: These disorders are caused when an individual has inherited the defective gene from a single parent. This defective gene belongs to an autosome. Such an inheritance is also known as autosomal dominant pattern of inheritance.

B. Autosomal Recessive Genetic Disorder: Such disorders manifest only when an individual has got two defective alleles of the same gene, one from each parent. These genetic disorders are inherited via the autosomal recessive pattern of inheritance.

C. Sex-Linked Disorders: These are disorders related to sex chromosomes or genes in them.

D. Multi-Factorial Genetic Disorder: Such disorders are the result of genetic as well as environmental factors.

1.6. Common Genetic Disorder in Humans: [12, 18]

1.6.1. Achondroplasia: It is an autosomal dominant genetic disorder which is the most common genetic cause of dwarfism. Individuals suffering from achondroplasia vary from 4 feet to 4 feet 4 inches in height. They have disproportionately short limbs. However, there is no intellectual disability. In this disorder, the cartilage, especially in the long bones, fail to convert into bones. It is caused due to mutation in the FGFR3 gene (located on chromosome 4, which codes for a protein that regulates transformation of cartilage to bone). Although, an individual may inherit the disorder from an affected parent, the disorder is usually the result of a mutation in the sperm or egg of a healthy parent. Achondroplasia can be detected before birth with the help of prenatal ultrasound. There is no treatment for this disorder. However, limb extending surgeries can be done, although this is a controversial issue.

1.6.2. Achromatopsia: It is an autosomal congenital recessive disorder which is characterized by visual acuity loss, colorblindness, light sensitivity and nystagmus. It is also known as rod monochromatism. The symptoms are first noticed in children at the age of six months when they exhibit nystagmus and photophobic activities. Achromatopsia is of two forms. The more severe form is known as compete achromatopsia. Those who exhibit milder symptoms are known to suffer from partial achromatopsia. Using optical and visual aids are useful in improving vision of those suffering from achromatopsia.

1.6.3. Acid Maltase Deficiency: It is an autosomal recessive disorder, in which the defect is in the gene for the acid maltase enzyme, which leads to accumulation of glycogen stored in muscles. Glycogen build up, weakens the muscles of a patient suffering from this disorder. This may affect respiratory muscles resulting in respiratory failure. It is also known as the Pompe Disease. Although, in childhood and adolescence the symptoms show slow progress and are less severe, infantile forms cause death within first year.

1.6.4. Albinism: Albinism is a congenital disorder in which there is little or completely no production of melanin in hair, skin and iris of the eyes. Hence albinos (people suffering from albinism) have light colored skin, hair and eyes. It is caused due to inheritance of recessive alleles from parents. This disorder can't be cured. However, the symptoms can be alleviated with the help of surgical treatment, vision aids and using device that provide
1.6.5. Alzheimer's disease: Alzheimer's disease is the most common form of dementia which is characterized by gradual memory loss, irritability, mood swings, confusion and language breakdown. Although, scientists are not unequivocal about the cause of this disease, the most widely accepted reason is the amyloid cascade hypothesis, that suggests excess production of a small protein fragment called Abeta (Aβ). Also known as Senile Dementia of the Alzheimer Type (SDAT) or simply Alzheimer's, this is a degenerative disease and scientists are yet to find its cure. However, balanced diet, mental exercises and stimulation are often suggested for prevention of disease. [13]

1.6.6. Angelman syndrome: It is a neurological disorder that was first described by a British pediatrician, Dr. Harry Angelman, in 1965. This disorder is marked by intellectual and developmental delays, severe speech impairment and problems in movement and balance, recurrent seizures and small heads. Children with Angelman syndrome typically have a happy demeanor. They are hyperactive with short attention span and show jerky hand movements. These children appear normal at birth. This genetic disorder in human is a classical case of genetic imprinting, in which the disorder is caused due to deletion or activation of the maternally inherited chromosome 15. Its sister syndrome is the Prader-Willi syndrome in which there is a similar loss or inactivation of the paternally inherited chromosome 15.

1.6.7. Bardet-Biedl Syndrome: It is a pleiotropic recessive genetic disorder that is characterized by obesity, polydactyly, deterioration of rod and cone cells, mental retardation and defect in the gonads and kidney disease. It is difficult to diagnose Bardet-Biedl Syndrome, specially in the young. As no cure is yet known for the disorder, treatment is concentrated on specific organs and systems.

1.6.8. Barth syndrome: A rare but serious sex linked genetic disorder, the Barth syndrome is caused due to mutations or alterations in the BTHS gene. The gene is located on the long arm of X chromosome. This disorder primarily affects the heart. Besides heart defects, Barth syndrome results in poor skeletal musculature, short stature, mitochondrial abnormalities and deficiency of white blood cells. There is no cure for this disorder. Treatment focuses on managing the symptoms and preventing infections [28].

1.6.9. Bipolar disorder: Also known as manic depressive disorder or bipolar affective disorder, individuals suffering from bipolar disorder suffer from highly elevated moods, referred to as mania or episodes of severe depression. Research shows that both genetic as well as environmental factors are responsible for this disorder. Medicines as well as psychotherapy is found to be useful in dealing with the severe mood swings associated with the disorder.

1.6.10. Bloom syndrome: Bloom syndrome is an autosomal recessive genetic disorder, which is characterized by a high frequency of breaks and rearrangements in the chromosomes of an affected person. Symptoms include short stature, butterfly shaped facial rash, high pitched voice, increased susceptibility to cancer, leukemia, respiratory illnesses and infections. Some may even show mental retardation. Like other genetic disorders in human, there is no treatment for Bloom's syndrome. All treatment is preventive in nature. This disease is more common in Ashkenazi Jews with a frequency of 1/100 individuals suffering from this disorder [28].

1.6.11. Color blindness: Color blindness refers to the inability of differentiating among certain colors. This can be genetically inherited and can also be caused due to damage to the eye, nerve or brain. As far as genetics is concerned, color blindness is most commonly the result of mutations in the X chromosome. However, research has shown that mutation in 19 different chromosomes can cause color blindness. There is no treatment to cure color blindness. However, certain types of tinted filters and contact lenses may enable an individual to differentiate colors.

1.6.12. Cri du Chat syndrome: Cri du Chat syndrome is caused due to deletion of short (p) arm of chromosome 5. Most cases of this disorder are not inherited. In such cases, they are caused due to spontaneous deletion of a segment of chromosome 5 during formation of egg or sperm or during early stages of fetal development. The syndrome gets the name from the characteristic high pitched cry of an infant that resembles the cry of a cat. Other symptoms are intellectual disabilities, delayed development, microcephaly (small head), low birth weight, typical facial features and weak muscle tones during infancy. No specific treatment is available for this disorder.

1.6.13. Cystic fibrosis: Cystic fibrosis is an inherited disease of the glands that secrete mucus and sweat. Cystic fibrosis causes the mucus to become thick and sticky that clogs various organs of the body, that results in other complications. It mostly affects lungs, liver, pancreas, sinuses, intestines and sex organs. Cystic fibrosis also causes excess loss of salts through sweat that results in dehydration, tiredness, weakness and elevated heart rate. This is an autosomal recessive disorder in which the mutation is caused in the CFTR gene. At present, there is no cure for cystic fibrosis. However, doctors treat the symptoms using antibiotic therapy along with other treatments that would clear the mucus that accumulates in different organs [13].

1.6.14. Down syndrome: Also called Trisomy 21 it is a genetic disorder in human that is the result of extra copy of chromosome 21, that a child inherits from his/her parent. This extra genetic material causes delays in mental as well as physical development of a child. Physical peculiarities caused due to this syndrome include a narrow chin, a prominently round face, protruding tongue, short limbs, the Simian crease and poor muscle tone. Almost 1 in every 800 to 1000 births may have genetic abnormality. The incidence of this disorder increases with maternal age. Amniocentesis during pregnancy or birth can detect this abnormality. Karyotyping test of a child confirms this syndrome, if done after birth. No specific cure is available. However, treatment of the health problems and training and special education of such individuals is of great help [13].

1.6.15. Duchenne muscular dystrophy: It is an X linked recessive
trait which is characterized by progressive degeneration of muscles that results in loss of ambulation and finally leading to death. It is one of the most prevalent muscular dystrophies that affect only males. Females are just the carriers and hence don't show the symptoms. The disorder is caused due to mutation in the gene DMD (located on X chromosome) that codes for protein dystrophin which is an important component of muscle tissue. Physical therapy is effective in lessening physical disabilities of children suffering from this disorder. Besides this, recent advancements in medicines are helping in extending lives of those affected. Stem cell research also shows promising developments in dealing with this form of muscular dystrophy.

1.6.16. Martin-Bell syndrome: Also known as the Martin-Bell syndrome or marker X syndrome, the Fragile X syndrome is the most common cause of inherited form of mental retardation. It is the result of trinucleotide repeat disorder, in which, the trinucleotide gene sequence CGG in the X chromosome is repeated several times. The result is intellectual disabilities, high levels of anxiety and hyperactivity like fidgeting, autistic behavior like hand flapping, avoiding eye contact, shyness, mental retardation and attention deficit disorder and other symptoms. It is an X-linked dominant disorder that has no cure. Medicines, educational, behavioral and physical therapy are the only help available to individuals suffering from this disorder.

1.6.17. Hemophilia: This is a recessive X-linked genetic disorder in which the bodies of individuals lose the ability to coagulate blood or blood clotting. As the mutation is caused in X chromosome and the condition is recessive, the females are carriers and males suffer from the symptoms of hemophilia. However, under rare occasions, females may also suffer from hemophilia. There are two variations of the disorder. Hemophilia A which is more common than the other variation, Hemophilia B. Regular infusion of the coagulating factor that lacks in an individual, helps one control blood loss caused due to excessive bleeding.

1.6.18. Huntington's disease: It is an autosomal dominant genetic disorder in the huntingtin gene, that produces a faulty protein instead of the normal "huntingtin" protein. The faulty protein causes damage to specific areas of the brain that initially manifests as abnormal involuntary movements that become increasingly uncoordinated jerky movements. As the disease progresses, decline on mental abilities (marked with dementia), behavioral and psychiatric problems become prominent. Although physical symptoms of Huntington's disease may manifest at any age, it most commonly occurs in individuals between 35 to 45 years old. In rare cases, when onset of the disease takes place as early as 20 years, the condition is referred to as juvenile, akinetic-rigid or Westphal variant HD. Although there is no cure, medicines help individuals to cope with emotional disabilities. Speech therapy, occupational and behavioral therapy also help individuals deal with the disabilities due to Huntington's disease.

1.6.19. Jackson-Weiss Syndrome: It is an autosomal dominant genetic disorder in which there are foot abnormalities, and premature fusion of bones in the skull lead to deformations of the facial features (widely spaced eyes, bulging forehead) and the skull. In this syndrome, the great toes are short and wide and turn away from the rest of the toes. Some toes may be fused or have some other abnormalities. The mutation is caused in the FGFR2 gene which is located in chromosome 10. Treatment involves corrective surgery for deformed bones in face and foot.

1.6.20. Klinefelter Syndrome: It is the most common sex linked genetic disorder. In which males have an extra X chromosome. Hence this disorder is also known as 47, XXY or XXY syndrome. The most common symptom is infertility. Besides this, males with the XXY syndrome have impaired physical, language and social developments. As these individuals produce less testosterone than other males, such teenagers may be less muscular and have less facial hair than their peers. The presence of the extra X chromosome can't be undone. However, testosterone replacement therapy, a variety of therapeutic options like behavioral, speech and occupational therapy and educational treatments are the options available for those suffering from Klinefelter's syndrome.

1.6.21. Krabbe disease: Krabbe disease is a rare degenerative disorder of the nervous system. It occurs due to mutation in the GALC gene which results in deficiency of enzyme galactosylceramidase. Deficiency of this enzyme affects the development of the myelin sheath of nerve cells. This disorder is inherited in autosomal recessive pattern and manifests itself in babies of 6 months of age. However, it can occur during adolescence or adulthood as well. Bone marrow transplant has help some who suffer from mild form of this disorder. Treatment is usually symptomatic and supportive.

1.6.22. Langer-Giedion syndrome: Langer-Giedion syndrome is a genetic disorder in human that is caused due to deletion or mutation of at least two genes on chromosome 8. This is not an inherited disorder. It is caused due to random events during formation of reproductive cells (sperms and eggs) in individuals. This is a rare disorder that causes bone abnormalities and typical facial features. Individuals suffering from Langer-Giedion syndrome have multiple non-cancerous tumors in their bones that cause pain, restrict joint movement and exerts pressure on nerves, blood vessels, spinal cord and the tissues surrounding the tumors. Some intellectual disability may be associated with this disorder. External fixators can be used for facial and limbic reconstructions.

1.6.23. Lesch-Nyhan syndrome: It is an X-linked recessive disorder which causes deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). Lack of HPRT leads to accumulation of uric acid in body, which leads to gout and kidney problems, poor muscle control and mental retardation of moderate degree. A striking feature of this disorder is a child biting his lips and fingers. This self-mutilating behavior appears in second year of a child's life. Other than these features, an individual suffering from this disorder shows facial grimacing, involuntary writhing and repetitive movement of limbs that is characteristic of Huntington's disease. This disorder is alternatively also known as Nyhan’s syndrome, Juvenile gout and Kelley-Seegmiller syndrome. Treatment for the Lesch-Nyhan syndrome is symptomatic.

1.6.24. Marfan syndrome: Marfan syndrome is an inherited
Muscular dystrophy: Muscular dystrophy (MD) refers to a group of genetically inherited disorders of progressive degeneration of skeletal muscles. It also causes defects in muscle proteins and death of muscle cells and tissues. These disorders vary in severity and the extent and distribution of muscle weakness. Although the skeletal muscles are primarily affected, muscular dystrophy may impair functions of other systems of the body as well. While in some cases the symptoms appear in infancy of childhood, in certain instances muscular degeneration sets in during adulthood. Duchenne MD is the most common form of MD. Other common disorders are Becker MD, Facioscapulohumeral MD and Myotonic MD. There is no specific treatment to cure or reverse MD. However, therapeutic options like speech therapy, respiratory therapy, speech therapy and corrective orthopedic surgery and orthopedic appliances are used to treat disabilities due to MD.

Myotonic dystrophy: Myotonic dystrophy, also known as dystrophia myotonica (DM) is an autosomal recessive genetic disorder that is caused due to repetition of a trinucleotide sequence. It affects the muscles of the body and is a multi-system disorder. Other than progressive muscle wasting, there is formation of cataracts in the eye, cardiac conduction defects and hormonal imbalances. There are two variations of this disorder – DM 1 and DM 2. DM 1 is more severe than DM 2. In DM 1 the trinucleotide sequence repeat is located on chromosome 9 whereas in case of DM 2 the trinucleotide sequence repeat occurs in chromosome 3. Although this disorder can manifest at any stage of one's life, variability with respect to age on onset of the symptoms reduces within successive generation. Hence it is a good example of anticipation. There is no cure for this disorder. Nevertheless the affected organs can be treated to manage the symptoms.

Nail-patella syndrome: Nail-patella syndrome (NPS) is inherited via autosomal dominant pattern. It is a disorder that affects the joints, bones, fingernails and kidneys. It is most commonly characterized by lack of nail and knee caps. Bone deformations manifest in elbow and abnormally shaped hip bone. Research shows that individuals suffering from the NPS are susceptible to developing glaucoma and scoliosis. Other names for NPS are hereditary onychostedysplasia, iliac horn syndrome, Fong disease or Turner-Kiser syndrome.

Neurofibromatosis: An autosomal dominant condition, neurofibromatosis (abbreviated NF) is a genetically inherited condition in which nerve tissue grow tumors, that may be benign or may cause medical complications by compressing nerves and tissues around them. Hence, in this disorder the bones, nervous system, the spine and the skin are affected. Tumors under the skin may appear as bumps and are associated with skin discoloration. Learning disabilities are also associated with this disorder. There are two types of this disorder. Neurofibromatosis type 1 is more common than neurofibromatosis type 2. While type 1 is caused due to mutation in chromosome 17, neurofibromatosis type 2 is the result of a mutation in chromosome 22. Due to lack of any cure, treatment is aimed at managing symptoms and complications. In case, the tumor becomes cancerous (as happens with 10% of the cases), chemotherapy may be required. Surgery is resorted to, when the tumor compresses any organ or specific tissue of the body.

Noonan syndrome: It is an autosomal dominant genetic disorder that may be inherited or arise due to spontaneous mutation in genes KRAS, PTPN11, RAF1, and SOS1. Individuals suffer from developmental disabilities that result in heart malformations, short stature, characteristic facial features, impaired blood clotting and indentation of the chest. Speech, language and learning disabilities are also common.

Osteogenesis Imperfecta: This is an autosomal dominant disorder of the connective tissue in which bones break easily and sometimes due to no apparent reason. Hence, it is also known as brittle bone syndrome or Lobstein disorder. Genetic mutation impairs synthesis of collagen - a protein that makes bones strong. Osteogenesis Imperfecta may also weaken muscles, cause brittle bones, curved spine and an impaired hearing. Exercise, physical therapy, medicines and orthopedic devices are the only treatment available for people suffering from this disorder, as cure hasn't yet been found.

Patau syndrome: Also known as trisomy D or trisomy 13, Patau syndrome is caused due to non-disjunction of chromosome 13 during meiosis, due to which, an affected individual inherits an extra copy of the chromosome. Robertsonian translocation can be another cause of this disorder. Like other genetic disorders in human that originate due to non-disjunction of chromosomes, the incidence of Patau syndrome increases with maternal age. The extra copy of chromosome results in kidney and heart defects, neurological problems, facial defects, polydactyly (having extra fingers) and deformed feet. Features of this disorder are present from birth and may be confused with Edward's syndrome. Hence, genetic testing is important to confirm diagnosis. While certain infants may be able to survive only for a couple of days, depending upon the severity of the conditions, those who survive with milder symptoms undergo treatment, focusing the particular disability that
each individual suffers from [2].

1.6.33. Phenylketonuria: (abbreviated as PKU) It is an autosomal recessive genetic disorder that causes deficiency in the enzyme phenylalanine hydroxylase. The result of this deficiency is that instead of being metabolized to tyrosine, the amino acid phenylalanine gets converted into phenylketone (also known as phenylpyruvate). This compound is detected in urine. If left untreated, excess phenylketone can impair development of the brain. This will manifest as mental retardation, seizures or brain damage [3].

1.6.34. Porphyria: Porphyria is an inherited genetic disorder in which, synthesis of any one of the 8 enzymes involved in the process of synthesis of heme, is disrupted. Heme is linked to a chemical called protoporphyrin. Disruption in the heme biosynthetic pathway results in accumulation of porphyrin or its precursors in the body that cause neurological or dermal problems. Acute porphyria affects the nervous system, whereas cutaneous porphyria or erythropoietic porphyria primarily affects the skin. This disorder is inherited in autosomal dominant pattern. Taking heme externally through a vein and medicines can alleviate the symptoms of this disorder.

1.6.35. Retinoblastoma: Retinoblastoma is a cancer of the retina that affects children younger than 5 years. It can be genetic as well as non-genetic. The genetic form, which is the cause in almost half of the cases of retinoblastoma, is the result of mutation in chromosome 13. Retinoblastoma usually affects one eye. Characteristic physical feature is whiteness of the retina, which is referred to as "cat's eye reflex" or leukocoria. Other symptoms include deterioration in vision, eye pain, redness and irritation in the eye. Retinoblastoma is curable if treated at an early stage. However, if not treated on time, cancer may spread out from the eye to other parts of the body.

1.6.36. Rett syndrome: Rett syndrome is a neurological and developmental disorder that is inherited through X-linked dominant pattern. It occurs almost exclusively in females. For about a year of normal growth, girls with Rett's syndrome show clinical features that include decreased rate of head growth, small hands and feet, disabilities related to learning, communication, coordination and speech. Affected girls lose control over purposeful use of hands and show repetitive movements like wringing of the hands and clapping.

1.6.37. Sickle cell anemia: Sickle cell disease or sickle cell anemia is a blood disorder which is inherited via autosomal recessive pattern. Mutation in the HBB gene, causes sickling of the red blood cells that may lead to a number of complications. Sickling causes the red blood cells to break down prematurely causing anemia and conditions related to it like, fatigue and shortness of breath. Severe anemia may delay development in children. Sickle cell disease makes one prone to infections and one may experience painful episodes when the sickled blood cells get stuck in small blood vessels. This deprives organs and tissues of enough oxygen and may cause damage to organs like lungs, kidney, spleen and brain. Life expectancy due to this disease is reduced to 42 years for males and 48 years for females. Bone marrow transplant and introduction of certain compounds like cyanate, penicillin and folic acid is used to manage complications due to this genetic disorder [13-14].

1.6.38. Tay-Sachs disease: It is an autosomal recessive genetic disorder that progressively destroys nerve cells in brain and the spinal cord, leading to neurological and physical disabilities. The most common form is the infantile Tay-Sachs disease that presents itself at the age of 3 to 6 months. These infants lose motor skills like ability to turn, sit or crawl. As the disease progresses, there is mental disability, vision and hearing loss, occurrence of seizures and paralysis. Such infants usually die within the initial years of childhood. Other forms of Tay-Sachs disease, that may affect adolescents and adults are rare and less severe. Sadly, there is absolutely no cure for the disease. The only help that a suffering child can be provided is, to make him as comfortable as possible till the disease has run its course.

1.6.39. Turner syndrome: Turner syndrome refers to a condition in which a woman lacks either one whole or a part of an X chromosome. The most characteristic feature of Turner syndrome is small stature that becomes evident when one is around 5 years old. Other symptoms include loss of ovarian functions, absence of menstrual cycle, swelling, broad chest, low hairline and webbed neck. Such women are prone to heart diseases, hypothyroidism, diabetes and visual and auditory problems. Since, this is a chromosomal abnormality, there is no cure. However, estrogen replacement therapy and doses of growth hormones are successful in minimizing the symptoms.

1.6.40. Usher's syndrome: Inherited in autosomal recessive pattern, Usher syndrome or Usher's syndrome is the result of mutation in chromosome 10, that results in deafness and progressive loss of vision. Vision loss is caused due to an eye disease called retinitis pigmentosa (RP), whereas hearing loss is associated with a defective inner ear. There are three clinical varieties of this disorder, designated as I, II and III in decreasing order of severity. Currently, no cure for this disease is available. However, gene therapy is being progressively investigated to find a possible cure. Till then, educational programs to facilitate communication, use of hearing aids or cochlear implants are some options to minimize the symptoms of this disorder.

1.6.41. Von Hippel-Lindau syndrome: Von Hippel-Lindau syndrome is a rare autosomal dominant genetic disorder in human that is characterized by the formation of tumors and fluid-filled sacs (cysts) in different parts of the body. The tumors are called hemangioblastomas that are typical of this disorder and consist of newly formed blood vessels and are typically noncancerous. The tumors when formed in brain or spinal cord cause headaches, vomiting and loss of muscle coordination. People suffering from this disorder are prone to developing cysts in the kidney, pancreas and the male genital tracts. The Von Hippel-Lindau syndrome is of two types. Type I is associated with low risk of developing tumors as opposed to the type II variety in which this risk is quite high [25-19].

1.6.42. Waardenburg Syndrome: Waardenburg Syndrome is an autosomal dominant genetic disorder that is characterized by
varying degrees of deafness and changes in hair and skin pigmentation. One of the most commonly observed features is eyes of different colors or brilliantly colored blue eyes. Cleft lip and/or cleft palate are also associated with this syndrome. Deafness arising due to the genetic defect is treated as any irreversible deafness would be. Other disabilities - physical or neurological are treated symptomatically [13].

1.7. Application of Gene Therapy:
Gene Therapy has made important medical advances in less than two decades. Within this short time span, it has moved from the conceptual stage to technology development and laboratory research to clinical translational trials for a variety of deadly diseases. Among the most notable advancements are the following:

1.7.1. Gene Therapy for Genetic Disorders
A. Severe Combined Immune Deficiency (ADA-SCID)
ADA-SCID is also known as the bubble boy disease. Affected children are born without an effective immune system and will succumb to infections outside of the bubble without bone marrow transplantation from matched donors. A landmark study representing a first case of gene therapy "cure," or at least a long-term correction, for patients with deadly genetic disorder was conducted by investigators in Italy. The therapeutic gene called ADA was introduced into the bone marrow cells of such patients in the laboratory, followed by transplantation of the genetically corrected cells back to the same patients. The immune system was reconstituted in all six treated patients without noticeable side effects, who now live normal lives with their families without the need for further treatment.

B. Chronic Granulomatous Disorder (CGD)
CGD is a genetic disease in the immune system that leads to the patients' inability to fight off bacterial and fungal infections that can be fatal. Using similar technologies as in the ADA-SCID trial, investigators in Germany treated two patients with this disease, whose reconstituted immune systems have since been able to provide them with full protection against microbial infections for at least two years.

C. Hemophilia
Patients born with Hemophilia are not able to induce blood clots and suffer from external and internal bleeding that can be life threatening. In a clinical trial conducted in the United States, the therapeutic gene was introduced into the liver of patients, who then acquired the ability to have normal blood clotting time. The therapeutic effect however, was transient because the genetically corrected liver cells were recognized as foreign and rejected by the healthy immune system in the patients. This is the same problem faced by patients after organ transplantation, and curative outcome by gene therapy might be achievable with immune-suppression or alternative gene delivery strategies currently being tested in preclinical animal models of this disease.

1.7.2. Gene Therapy for Acquired Diseases [6, 11, 17, 24]
A. Cancer
Multiple gene therapy strategies have been developed to treat a wide variety of cancers, including suicide gene therapy, oncolytic virotherapy, anti-angiogenesis and therapeutic gene vaccines. Two-thirds of all gene therapy trials are for cancer and many of these are entering the advanced stage, including a Phase III trial of Ad.p53 for head and neck cancer and two different Phase III gene vaccine trials for prostate cancer and pancreas cancer. Additionally, numerous Phase I and Phase II clinical trials for cancers in the brain, skin, liver, colon, breast and kidney among others, are being conducted in academic medical centers and biotechnology companies, using novel technologies and therapeutics developed on-site. Gene therapy is useful for glioblastomas because the cells do not spread throughout the body as other tumor cells do, so treatment can be localized. Another advantage is that the body's immune defenses in the brain are weak, so the rejection to the mouse cells is not quite as dramatic as elsewhere. Another approach to cancer therapy is to replace a damaged p53 gene, the tumor suppressing gene. The normal gene helps repair DNA damage in the cell, but when it is in the mutated form, the gene cannot perform its function and a tumor develops. Researchers are now investigating the possibility of using adenoviruses (to be discussed presently) to deliver correct copies of the p53 gene to patients with liver cancer. At this writing, a limited number of tests have been performed, with encouraging results [17, 24].

B. Blindness
Leber's congenital amaurosis (LCA) is a rare inherited eye disease that appears at birth or in the first few months of life, and affects around 1 in 80,000 of the population. It was first described by Theodore Leber in the 19th century. LCA is typically characterized by nystagmus, sluggish or no pupillary responses, and severe vision loss or blindness. Researchers at Moorfields Eye Hospital and University College London in London conducted the first gene therapy clinical trial for patients with RPE65 LCA. The first patient was operated upon in early 2007. Researchers at Children's Hospital of Philadelphia and the University of Pennsylvania have treated six young people via gene therapy.

C. Neurodegenerative Disease
Recent progress in gene therapy has allowed for novel treatments of neurodegenerative diseases such as Parkinson's Disease and Huntington's Disease, for which exciting treatment results have been obtained in appropriate animal models of the corresponding human diseases. Phase I clinical trials for these neurodegenerative disorders have been, or will soon be, launched [15, 19].

D. AIDS
Gene therapy may also be used one day to relieve the effects of acquired immune deficiency syndrome (AIDS). Clinical tests have been approved for a novel gene transfer therapy for persons infected with HIV. The test involves a mutant strain of HIV containing defective forms of the genes rev and env. This strain was produced by researchers at the University of California at San Diego. The new HIV strain cannot replicate because rev and env genes encode regulatory viral protein and envelope protein, both of which are essential for viral replication. To use the viruses as therapeutic devices, researchers remove T-lymphocytes from HIV-infected patients and insert the mutated viruses into the cells. Then they cultivate large numbers of the cells and inject them back into the patient. The virus-containing T-lymphocytes cannot produce viruses, but they do stimulate the body to produce cells called CD8
killer lymphocytes. These killer cells are specifically manufactured to interact with HIV infected cells, and in laboratory tests they destroy those cells. Another form of gene therapy involves attaching genes for HIV proteins to the DNA of mouse viruses, which are harmless for humans. The transformed viruses are then injected into individuals, who are infected with HIV but display no symptoms of disease. Researchers believe that the HIV genes will stimulate the normal body cells to produce HIV proteins. The proteins should stimulate the immune system to secrete anti-HIV antibodies. These antibodies may be useful in preventing HIV replication in the patient and forestalling the T-lymphocyte destruction that characterizes AIDS. Still another possible form of anti-AIDS therapy involves a process that works in the laboratory but has been used in limited clinical trials to date.

1.8. Gene Therapy Products in market

Due to the various economic and political reasons, China was the first country moving on with the gene therapy commercialization. Both of the currently available products (Oncorine™ and Gendicine™) have their Western counterparts, but the acceptance process and results from the treated patients have raised concerns over different scientific and regulatory standards during the process. Interestingly, currently SiBiono Gene Technologies is owned by US listed Benda Pharmaceuticals and Sunway Biotech is owned by US Mergen Biotech. It remains to be seen whether these product will be expanded to Western markets at some point. [12, 16, 17]

1.8.1. Gendicine

Gendicine™, a p53 adenovirus for the treatment of head- and neck squamous cell cancer is used in combination with radiotherapy. After the approval of Gendicine™ by the SFDA, there has been intensive discussion about the efficiency of the treatment and lack of details in the reporting.

1.8.2. Oncorine

Oncorine™ for treating head and neck cancer (H101) is a conditionally replicative adenovirus, with a deletion in E1B 55K region [17, 28], therefore restricting the virus to bind and inactivate wild-type p53 protein. Inactivation of the host cell p53 is essential for wild-type adenoviruses to disable the activation of apoptotic pathways when host cell shifts to S phase in the lytic infection. When E1B 55K activity is removed, the replication in normal cells is blocked, allowing only replication in p53-deficient cells. In malignant cells the viral proliferation leads to oncolysis, used as a cancer therapy to treat solid tumours [27, 28].

1.8.3. Cerepro®

Cerepro® (Sitimagene ceradenovac) from Anglo-Finnish Company Ark Therapeutics Group PLC is an adenovirus containing a Herpes simplex type-1 thymidine kinase transgene, under the cytomegalovirus promoter, for the treatment of malignant glioma together with ganciclovir. The company claimed an Orphan Drug status for Cerepro® from EMA and FDA.

1.8.4. Glybera

Glybera® from AMT biopharma is an adeno-associated virus containing S447X mutated LPL transgene with CMV-WPRE promoter for lipoprotein lipase deficiency. LPLD is a seriously debilitating, and potentially lethal, orphan disease. The disease is caused by mutations in the LPL gene, resulting in highly decreased or absent activity of LPL protein in patients. Recurrent pancreatitis in LPLD patients can result in difficult-to-treat diabetes.

1.9. Future Prospective:

Looking to the future, it will also be important that injectable vectors are widely available so that multidisciplinary teams (biochemists, physicians, surgeons, and specialized hospital personnel) are not needed to administer gene therapy. [29] The challenge of developing successful gene therapy for any specific condition is considerable:

- The condition in question must be well understood
- The underlying faulty gene must be identified and a working copy of the gene involved must be available
- The specific cells in the body requiring treatment must be identified and accessible

1.10. Summary & Conclusion:

The concept of gene regulation will be a continuing issue because, although regulation is not critical in diseases now being treated, it will become a key factor in dealing with such diseases as diabetes. And the debate about gene insertions into somatic cells and reproductive cells will be revisited as protocols for insertions into reproductive cells are developed. Resolving these issues is a formidable task, which is why exaggerated hopes for gene therapy should always be tempered with realism. Nevertheless, W. French Anderson, the NIH researcher at the forefront of gene therapy was quoted in 1995 as saying: "Twenty years from now, gene therapy will have revolutionized the practice of medicine. Virtually every disease will have (gene therapy) as one of its treatments." Stay tuned.

2. Reference:


