GENE THERAPY

ANIL KUMAR
School of Biotechnology
Devi Ahilya University
INDORE-452017, INDIA
Ph No: +91-731-2470372, 2470373
Fax No: +91-731-2470372.
E-Mail: ak_sbt@yahoo.com,
        bioinfo@sancharnet.in
URL: www.davvbiotech.res.in
Introduction

Gene therapy is the process by which DNA sequences encoding specific genes are delivered to cells with the aim of treating or curing a disease. The concept of gene therapy developed within the perspective of “molecular medicine” as it became evident that many diseases arise because of an individual is deficient for a critical protein that is encoded by a particular gene. Since each protein is produced according to instructions encoded in the corresponding gene, such diseases arising from mutations in genes were designated as “genetic diseases”. Classical examples of such diseases (with a genetic origin) are forms of diabetes due to lack of insulin (a protein hormone), Duchenne muscular dystrophy (mutation in gene coding for dystrophin, cell membrane protein in muscle cells), hemophilia due to the lack of factor VIII or factor IX (proteins required for blood clotting). Factors VIII and IX are synthesized in the liver and participate in the chain of events that produces a long fibrous protein called fibrin that serves as the matrix for blood clot formation.
In hemophilia, Minor cuts and bruises, which would do little harm to most people, can prove fatal to hemophiliacs, who lack the proteins (Factors VIII and IX) involved in the clotting of blood, which are coded by the defective genes. Sadly, before these proteins were made available through genetic engineering, hemophiliacs were treated with protein isolated from human blood. Some of this blood was contaminated with the AIDS virus, and has resulted in tragic consequences for many hemophiliacs. Now, use of genetically engineered proteins in therapeutic applications is common rather than blood products. Often a mutation occurs in gene that eliminates the formation of such a protein in a functional form resulting in a disease state. Therefore, **gene therapy concerns the possibility of delivering a normal gene to the tissues or taking corrective measures to where a mutant gene has rendered the corresponding protein non-functional.**
What is Gene Therapy

- A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene. This approach is most common.

- An abnormal gene could be swapped for a normal gene through homologous recombination.

- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function.

- The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.
If the gene therapy is successfully achieved, the individual suffering from a genetic disease would have the deficiency corrected and lead a normal life. Recent advances in Genomics and Molecular Biology have revealed that almost all diseases have a genetic component. In cystic fibrosis or hemophilia mutations in a single gene result in disease. Whereas in hypertension or high cholesterolemia, certain genetic variations may interact with environment stimuli to cause disease. Pathological conditions associated with ageing frequency result from the loss of gene activity in specific types of cells.

Some single gene disorders are quite common—cystic fibrosis is found in one out of every 2,500 babies born in the Western World—and in total, diseases that can be traced to single gene defects account for about 5% of all admissions to children’s hospitals. It is expected that the genetic disease may be corrected with the use of gene therapy.
The first example of gene therapy in a mammal was the correction of the growth hormone deficiency in mice. The recessive mutation little (lit) results in dwarf mice, even though the mouse growth hormone gene is present and apparently normal, no messenger RNA (mRNA) is produced. The initial step in correcting this deficiency was to inject homozygous lit that is lit eggs with about 5000 copies of a 5-kb linear DNA fragment that contained the rat growth hormone structural gene (RGH) fused to a regulator promoter sequence from a mouse metallo-protein gene (MP).
The eggs were then implanted into pseudo-pregnant mice, and the baby mice were raised. About 1% of these babies turned out to be transgenic, showing increased size when heavy metals were administered during development. A representative transgenic mouse was then crossed to a *it lit* female. The site of insertion of the introduced DNA in mammals is highly variable, the DNA is generally not found at the homologous locus.
Diseases of Genetic Origin

There are exciting new programs to map the entire human genome. This work will enable scientists and clinicians to understand the genes that control all diseases to which the human race is prone, and hopefully develop new therapies to treat and credit diseases. If the gene is dominant, it alone can produce the disease in the couples even if its counterpart is normal, thus the children of a parent with the disease can be affected; Huntington’s chorea, a severe disease of the nervous system, which becomes apparent only in adulthood, is an example of a dominant genetic disease. 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 most likely candidates for future gene therapy trials will be rare diseases such as Lesch-Nyhan syndrome a distressing disease in which the patients are unable to manufacture hypoxanthine-guanine phosphoribosyl transferase enzyme. This leads to a bizarre impulse for self-mutilation, including very severe biting of the lips and fingers. The normal version of the defective gene in this disease has now been cloned.
Types Of Gene Therapy

Gene Augmentation Therapy

The traditional approach to gene therapy is to introduce DNA to the genome to replace a defective DNA/gene fragment that has lost normal function, and can be described as gene augmentation therapy (GAT). The aim of gene augmentation therapy is to correct a loss of function caused by a deletion by adding the functional allele. Transferred genes may be stably integrated in to the genome with the potential to permanently correct the defect, especially if the stem cells transformed may be maintained episomally (an inevitable decay in the maintenance of gene expression and treatment may need to be repeated). Several GAT clinical trials are currently underway for diseases including cystic fibrosis, adenosine deaminase deficiency and familial hypercholesterolemia.
Gene Inhibition Therapy at the nucleic acid level

For the treatment of dominant genetic disease mutations causing loss of gene function or mutations that lead to some gain of function, gene augmentation therapy is less powerful. In principle, a valid approach to the treatment of such diseases would be targeted correction (i.e. allele replacement or gene knockout to remove the mutant allele). However, this is a very inefficient process in practice, even in cultured cells, and its application to the correction of genetic defects in many somatic cells, especially in vivo, demands further technical improvements. A novel approach, in future, is targeted correction at the RNA level by using ribozymes or RNA editing enzymes to correct pathogenic mRNAs.
An alternative strategy, which is presently undergoing clinical trials for the treatment of several types of cancer, is the use of nucleic acids to inhibit gene expression. The advantage of this approach is that the inhibitor can be synthesized or developed to inhibit the specific allele, without effecting the expression of any normal functioning allele. The introduction of antisense genes allows the stable and permanent expression of antisense RNA, which binds to (mutant) mRNA and prevents translation (it may also target the mutant mRNA for degradation). Furthermore, increasing use is being made of antisense construct containing ribozymes, which degrade the mRNAs to which they bind.
Oligonucleotides can be used for epigenetic gene therapy (i.e. therapy which does not involve changes to the genome) and can act in two ways. Antisense oligonucleotides act in the same way as antisense RNA, by binding to mRNA and causing inhibition and degradation (in this case, probably by recruiting RNase which digest the RNA strand of DNA: RNA hybrids).

Secondly, pyrimidine rich oligonucleotide can potentially form triple helix structures with purine rich strands of DNA (by Hoogsteen base pairing), which blocks transcription (triple helix therapy). Peptide Nucleic Acid (PNA) is an analog of DNA where the phosphate backbone is replaced by a neutral peptide backbone. PNA Oligonucleotides can be used as probes as well as agents for gene therapy. They form very stable triple-helix structures.
**Gene inhibition therapy at the protein level**

Targeted inhibition of gene expression can also take effect at the protein level. The cell is made to express within a cell of genetically engineered antibodies (intrabodies) which bind to and inactivate mutant proteins. Antibodies are not the only molecules being developed for protein level gene therapy. Any protein acting as multimer is a potential target for dominant negative inhibitor proteins, and this strategy is being explored to prevent viral coat protein assembly, including that of the HIV. A novel approach is to use degenerate oligonucleotides to identify specific oligonucleotide sequences, which interact with proteins. These Oligonucleotides or aptamers can then be used to inactivate specific mutant proteins.
Somatic Gene therapy focuses only on the body, or soma, attempting to effect a reversal of the disease phenotype by treating some somatic tissues in the affected individual. At present it is not possible to render entire body transgenic, so the method addresses disease whose phenotype is caused by genes that are expressed predominantly in one tissue. In such cases it is found that not all the cells of that tissue need to become transgenic; a portion of transgenic cells can ameliorate the overall disease symptoms. The methods proceed by removing some cells from an individual with the defective genotype and making these cells transgenic through the introduction of copies of the cloned wild type gene.
The cells are then reintroduced into the patient’s body, where they provide normal gene function. This is ex vivo gene therapy, gene transfer is performed in cells that have been removed from the patient. Once the therapeutic gene has been introduced into these cells they are transferred back to the patient.

For In vivo gene therapy approaches, genes are transferred into cells within the patient’s body. The route of administration depends on the target tissue that needs to be treated as well as the mechanism through which the therapeutic gene elicits its effect. For example, gene therapy vectors for cystic fibrosis, a disease which effects cells within the lung and airway, are inhaled.
Most gene therapies under evaluation to treat cancer are injected directly into tumors. Secreted proteins, such as Factor VIII or Factor IX for hemophilia or insulin for diabetes, may be introduced into the liver or muscle tissue.

Another approach to germinal gene therapy is the more ambitious to introduce transgenic cells into the germ line as well as into the somatic cell population. We have seen that such germinal therapy has been achieved using mice eggs. However, the protocol that is more relevant for application to humans is removal of an early embryo (blastocyst) with a defective genotype from a pregnant mouse and injection with transgenic cells containing the wild type allele.
These cells become part of many tissues of the body, often including the germ line, which will give rise to the gonads. Then the gene can be passed on to some or all progeny, depending on the size of the clone of transgenic cells that lodges in the germinal area. However, no human germinal gene therapy has been performed to date.

Beyond simply replacing a gene, a further phase can also be considered that encompasses gene therapy, but is more precisely called cell therapy.

In several hundreds of cases during the last decade, individuals with sickle cell anemia were “cured” for their lifetime (but they could still pass the mutated gene on to their children, although in this case without severe consequences if the other parent is normal) by bone marrow transplant.
This procedure is similar to other forms of organ transplant in which the individual must also be treated with drugs that suppress immune responses in order to reduce the risk of rejection due to tissue incompatibility. In such procedures the donor is usually a close relative without the sickle mutation. In July 2000, a group in Edmonton, Canada reported treating diabetic patients by injecting normal pancreatic cells from brain-dead donors into the livers of the seven treated patients. These patients must also be maintained on drugs that reduce the risk of rejection, but have been able to live without insulin treatment for months following the operation.
Gene Delivery Systems

The problem of delivering a gene to a target cell is one of the principal obstacles that must be overcome for gene therapy. Since viruses are known that efficiently infect cells, the use of such viruses has generally been considered as the promising technique for delivering genes. In all cases, the virus is modified in such a way as to destroy its capacity to transmit disease or harm the cell and the gene to be delivered is incorporated into the genetic material of the virus. This new virus is called a "vector" since it can transfer the gene to the target cell. Once inside the cells of the individual treated (the host), the viral DNA recombines with host DNA and is thus integrated into the host chromosome.
The success of this approach has been limited for several reasons. First, the genes delivered by the viruses do not always work as well in the target cells as was hoped, since they are not necessarily used by the cell to produce sufficient amounts of the needed protein. Although the gene may well be inserted into the DNA of the target cells, not all positions on the chromosome permit gene expression (i.e. transcription and translation into protein) with the same efficiency. Therefore, additional developments are required to target the genes transferred to portions of the chromosome that lead to more active expression.
In addition, compared to blood cells, most other types of cells are difficult to isolate or target by the vector. Moreover, in certain cases, an immunological reaction is generated against the virus that limits its usefulness. Following the deaths of patients in recent trials in the United States it is now widely accepted that further studies on animal models are needed and that human subjects should only be considered under very favorable circumstances, such as were available to the group of Fischer in their work on SCID (severe combined immunodeficiency disease).
As the genetic and molecular basis for a multiplicity of diseases is elucidated, the promise of gene therapy continues to grow. Although initial efforts in gene therapy focused on delivering a normal copy of a missing or defective gene, current programs are applying gene delivery technology across a broader spectrum of disease conditions. Gene delivery is now being used to:

- Replace missing or defective genes
- Deliver genes that catalyze the destruction of cancer cells or cause cancer cells to revert back to normal tissue
- Deliver viral or bacterial genes as a form of vaccination
- Deliver genes that promote the growth of new tissue or stimulate regeneration of damaged tissue.
The application of gene delivery technology to a growing roster of clinical indications is predicted on significant advances in both Genomics and gene delivery systems. As an increasing number of genes are identified and assigned to specific biochemical pathways, the therapeutic utility of these genes becomes more apparent. In parallel with an enhanced understanding of the roles that genes play in health and disease, improved vehicles, or vectors, for delivering therapeutic genes to target cells have been constructed. A growing number of genes are being evaluated for use as therapeutics.
A few genes evaluated are given in the table below:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Indication</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTR</td>
<td>Cystic Fibrosis</td>
<td>Regulates intracellular chloride</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Hemophilia A</td>
<td>Regulates blood coagulation</td>
</tr>
<tr>
<td>Factor IX</td>
<td>Hemophilia B</td>
<td>Regulates blood coagulation</td>
</tr>
<tr>
<td>E1A</td>
<td>Cancer</td>
<td>Causes cancer cells to undergo cell death or revert to normal</td>
</tr>
<tr>
<td>P53</td>
<td>Cancer</td>
<td>Causes cancer cells to undergo cell death</td>
</tr>
<tr>
<td>AC6</td>
<td>Heart Failure</td>
<td>Increases contractile properties of the heart</td>
</tr>
<tr>
<td>VEGF</td>
<td>Coronary artery disease</td>
<td>Peripheral vascular disease induces the growth of new blood vessels</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Cancer</td>
<td>Stimulates the immune system to kill cancer cells</td>
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Therapeutic genes can be introduced into target cells in a variety of ways. Gene delivery can be undertaken in cells that have been removed from the body (ex vivo gene therapy) or in the body itself (in vivo gene therapy). Genes can be introduced into cells using viruses, lipid-based (synthetic) vectors, naked DNA or electroporation (the application of an electrical charge, which creates opening in cell membranes). The selection of a particular delivery vehicle depends on a number of factors, including target cell type, duration of gene expression required for therapeutic effect, the size of DNA encoding the therapeutic gene and the route of administration. While no single vector developed to date is optimal for all clinical indications, the growing number of viral and synthetic vectors will enable gene therapy to be used in treating a wide variety of significant diseases.
Viral Vectors

Currently there are two ways of getting the trans-gene into the defective somatic cells. Both methods use viruses. The older method uses a disarmed retrovirus with the trans-gene spliced into its genome, replacing most of the viral genes. The natural cycle of retroviruses involves integration of the viral genome at some location in one of the host cells chromosomes. The recombinant retrovirus will carry the trans-gene along with it into the chromosome. This is a potential problem because the integrating virus can act as an insertional mutagen and inactivate some unknown resident gene, causing a mutation. This procedure has been used for somatic gene therapy of severe combined immunodeficiency disease (SCID).
In the gene therapy, blood stem cells were removed from the bone marrow, the transgene was added and the transgenic cells were reintroduced into the blood system.

Another vector used in human gene therapy is adenovirus. This virus normally attacks respiratory epithelia, injecting its genome into the epithelial cells. The viral genome does not integrate into a chromosome but persists extrachromosomally in the cells. This eliminates the problem of insertional mutagenesis by the vector. Another advantage of adenovirus as a vector is that it attacks nondividing cells, making most tissues susceptible in principle.
Since cystic fibrosis is a disease of the respiratory epithelium, adenovirus is an appropriate choice of vector for treating this disease, and gene therapy for cystic fibrosis is currently being attempted using adenovirus. Viral vectors take advantage of a virus ability to enter cells and deliver genetic material to the nucleus. In developing viral vectors, DNA encoding some or all of the viral genes is removed and is replaced with a therapeutic gene.

Most viral vectors also are engineered so that they are able to enter cells but lose their ability to replicate once inside. Based on the virus, from which it is derived, each type of viral vector has the ability to enter specific types of cells. While first generation viral vectors were thus restricted in their utility, newer vectors have been modified to meet specific objectives.
In some cases this may mean engineering the vector so that it enters only one cell type while in other situations an expanded targeting capability may be desired. Modifications are made by changing some of the proteins that are expressed on the virus surface. These proteins interact with other molecules on the surface of target cells, similar to a lock-and-key combination. In addition to varying targeting properties, different vectors have specific characteristics that regulate whether they permanently become part of the host cell’s genetic material or exist transiently within the host cell. Depending on the therapeutic aim of a particular gene therapy, persistent or transient expression may be more or less desirable.
Synthetic Vectors

In addition to using viruses as vectors for gene delivery, a variety of non-viral vectors also are under development. These synthetic vectors generally are made up of lipids (fat molecules). Cell membranes contain a very high concentration of lipids. When a synthetic vector encounters the membrane of a cell, the lipids in the vector are incorporated into the lipids of the membrane, allowing the DNA contained within the vector to gain entry to the cell. This process is similar to how droplets of fat floating on water coalesce to form larger drops. While some synthetic vectors encompass a circle of DNA carrying a therapeutic gene, other systems also compact the DNA.
This compaction makes the vector particles smaller and of more uniform size. Just as a cell contains proteins and other molecules embedded in the lipids of its membrane, synthetic vectors can be engineered to carry targeting molecules on their surfaces. Such targeting moieties allow synthetic vectors to be directed to specific types of cells, which is important from the standpoint of both safety and systemic delivery.
In addition to choosing a relevant therapeutic gene and the appropriate gene delivery system, the ability to express (turn on) the delivered gene is a key factor in the development of successful gene therapies. Current approaches utilize a variety of promoters, DNA sequences that act as on/off switches for gene expression. Some promoters are active only in specific cell types, and are used to target gene activity to specific cells. Other promoters are expressed in a wide variety of cell types and may be used when cell-specific expression is not required.
Promoter selection also depends on the level of gene expression desired. Inducible promoter systems, which can be turned on or off in response to certain drug or compounds, also are being investigated, as are self-regulating expression systems that provide very high levels of expression. The variety of gene expression systems available and under development expands the potential applications of gene therapy to new indications.
Routes of Administration

Even after the gene, vector and expression system have been optimized, the route through which a gene therapeutic is administered influences the therapeutic effect of the product.

Potential Benefits of Gene Therapy

A primary benefit of gene therapy is the ability to correct the underlying cause of genetic diseases. To date, the majority of therapeutics available for diseases such as cystic fibrosis, hemophilia and Gaucher’s disease only palliates disease symptoms. The delivery of functional copies of the genes involved in these diseases provides a mechanism through which the disease may be corrected at the molecular level.
Gene therapy also holds the potential to provide patient-friendly treatment regimens for a variety of diseases. Today, patients with hemophilia, diabetes and other diseases that are treated by the administration of therapeutic proteins must take daily or weekly injections in order to manage their disease. This is because proteins exist in the bloodstream for a limited period of time before they are degraded or eliminated. Because DNA is more stable and functions inside the cell, the delivery of therapeutic genes may result in long term expression of therapeutic proteins. Dosing regimens for gene therapy products are likely to require treatment every few weeks or every few months.
In the area of cancer therapeutics, gene therapy has the potential to eliminate cancer cells without damaging normal, healthy tissue. In clinical studies to date, cancer gene therapies have been shown to be well tolerated and have a good safety profile. Cancer gene therapies may provide therapeutic alternatives to patients whose disease does not respond to standard treatment regimens. Additionally, cancer gene therapies may enable patients to maintain a better quality of life during treatment than do chemotherapeutic agents or radiation therapy. As the genomics revolution identifies new genes and as gene delivery technologies continue to evolve, the role of gene therapy in the treatment of a wide variety of diseases is likely to grow.
What is current status of gene therapy research

In 1999, gene therapy suffered a major setback with the death of 18-year-old Jesse Gelsinger. Jesse was participating in a gene therapy trial for ornithine transcarboxylase deficiency (OTCD). He died from multiple organ failures 4 days after starting the treatment. His death is believed to have been triggered by a severe immune response to the adenovirus carrier.

Another major blow came in January 2003, when the FDA placed a temporary halt on all gene therapy trials using retroviral vectors in blood stem cells. FDA took this action after it learned that a second child treated in a French gene therapy trial had developed a leukemia-like condition. Both this child and another who had developed a similar condition in August 2002 had been successfully treated by gene therapy for X-linked severe combined immunodeficiency disease (X-SCID), also known as "bubble baby syndrome."
What factors have kept gene therapy from becoming an effective treatment for genetic disease?

- **Short-lived nature of gene therapy** - Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy.
**Immune response** - Anytime a foreign object is introduced into human tissues, the immune system is designed to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a potential risk. Furthermore, the immune system's enhanced response to invaders it has seen before makes it difficult for gene therapy to be repeated in patients.

**Problems with viral vectors** - Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient -- toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease.
- **Multigene disorders** - Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes. Multigene or multifactorial disorders such as these would be especially difficult to treat effectively using gene therapy.
What are some recent developments in gene therapy research?

- A team of British doctors from Moorfields Eye Hospital and University College in London conduct first human gene therapy trials to treat Leber's congenital amaurosis, a type of inherited childhood blindness caused by a single abnormal gene. The procedure has already been successful at restoring vision for dogs. This is the first trial to use gene therapy in an operation to treat blindness in humans. Blindness at www.reuters.com (May 01, 2007).

- A combination of two tumor suppressing genes delivered in lipid-based nanoparticles drastically reduces the number and size of human lung cancer tumors in mice during trials conducted by researchers from The University of Texas M. D. Anderson Cancer Center and the University of Texas Southwestern Medical Center. Dual Gene Therapy Suppresses Lung Cancer in Preclinical Test at www.newswise.com (Jan.11, 2007).
Researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, successfully reengineer immune cells, called lymphocytes, to target and attack cancer cells in patients with advanced metastatic melanoma. This is the first time that gene therapy is used to successfully treat cancer in humans.


Gene therapy is effectively used to treat two adult patients for a disease affecting nonlymphocytic white blood cells called myeloid cells. Myeloid disorders are common and include a variety of bone marrow failure syndromes, such as acute myeloid leukemia. The study is the first to show that gene therapy can cure diseases of the myeloid system.

Gene Therapy Appears to Cure Myeloid Blood Diseases at [www.cincinnatichildrens.org](http://www.cincinnatichildrens.org) (March 31, 2006)
Gene Therapy cures deafness in guinea pigs. Each animal had been deafened by destruction of the hair cells in the cochlea that translate sound vibrations into nerve signals. A gene, called *Atoh1*, which stimulates the hair cells' growth, was delivered to the cochlea by an adenovirus. The genes triggered regrowth of the hair cells and many of the animals regained up to 80% of their original hearing thresholds. This study, which many pave the way to human trials of the gene, is the first to show that gene therapy can repair deafness in animals.

Gene Therapy is First Deafness 'Cure' at NewScientist.com (February 11, 2005)
University of California, Los Angeles, research team gets genes into the brain using liposomes coated in a polymer called polyethylene glycol (PEG). The transfer of genes into the brain is a significant achievement because viral vectors are too big to get across the "blood-brain barrier." This method has potential for treating Parkinson's disease.

RNA interference or gene silencing may be a new way to treat Huntington's. Short pieces of double-stranded RNA (short, interfering RNAs or siRNAs) are used by cells to degrade RNA of a particular sequence. If a siRNA is designed to match the RNA copied from a faulty gene, then the abnormal protein product of that gene will not be produced.

Gene Therapy May Switch off Huntington's at NewScientist.com (March 13, 2003)
New gene therapy approach repairs errors in messenger RNA derived from defective genes. Technique has potential to treat the blood disorder thalassaemia, cystic fibrosis, and some cancers.

Gene therapy for treating children with X-SCID (severe combined immunodeficiency) or the "bubble boy" disease is stopped in France when the treatment causes leukemia in one of the patients.

Researchers at Case Western Reserve University and Copernicus Therapeutics are able to create tiny liposomes 25 nanometers across that can carry therapeutic DNA through pores in the nuclear membrane.

Sickle cell is successfully treated in mice.
Another Death in a Gene Therapy Trial

Health Care Renewal, August 01, 2007

The case of the death of a research subject in an early trial of gene therapy for arthritis raises some eerie parallels to previous cases. So far the case has sparked minimal media attention, so although the news so far raises far more questions than answers, it appears worth summarizing on Health Care Renewal.

Some 127 patients have received an initial dose of the active drug or placebo, including 74 that received a second dose of the drug, Targeted Genetics said. The drug, known as tgAAC94, is designed to be used along with other therapies. The Scientist provided a little more detail about the therapeutic intervention.
Researchers in the field say the treatment's delivery vector, an adeno-associated virus (AAV), was unlikely to be the culprit.

'Vectors in this class have been used on hundreds of patients over the last 12 years, and are not associated with acute toxicity,' said Terence Flotte of the University of Massachusetts Medical School in Worcester. Flotte has been a principal investigator in several clinical trials of AAV-based gene therapy, but is not associated with the trial in question. 'I've never seen anything like this,' he told The Scientist. 'Whatever this is, it's unusual.'
In the trial, the AAV vector delivered a transgene encoding the receptor for tumor necrosis factor (TNF)-alpha, a cytokine that causes joint swelling in arthritis patients. The receptor, secreted by the target cells, binds to TNF-alpha, to reduce inflammation and protect the joint.

Usually prescribed for autoimmune conditions such as rheumatoid arthritis, the TNF-alpha receptor works by suppressing the immune system. But the protein could also have opened the door to an infection, suggested Flotte.
Wilson, owner of 30% of Genovo Stock reportedly made $13.5 million from the sale of the Co. to Targeted Genetics says:

It's too early to tell what this case means, but I do have some comments. Just because a treatment has been used on "hundreds" of patients does not mean that it has no serious acute side-effects. It only means that such side-effects may be relatively infrequent.