Gene therapy

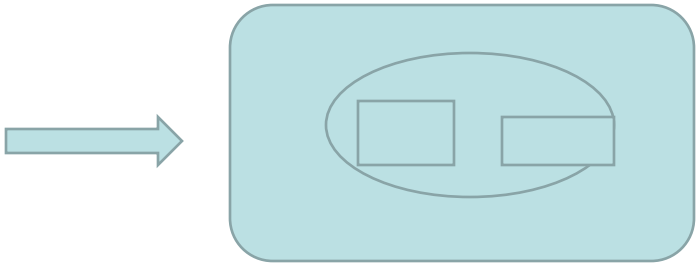
Dr. Imran Riaz Malik
Health Biotechnology

What is gene therapy

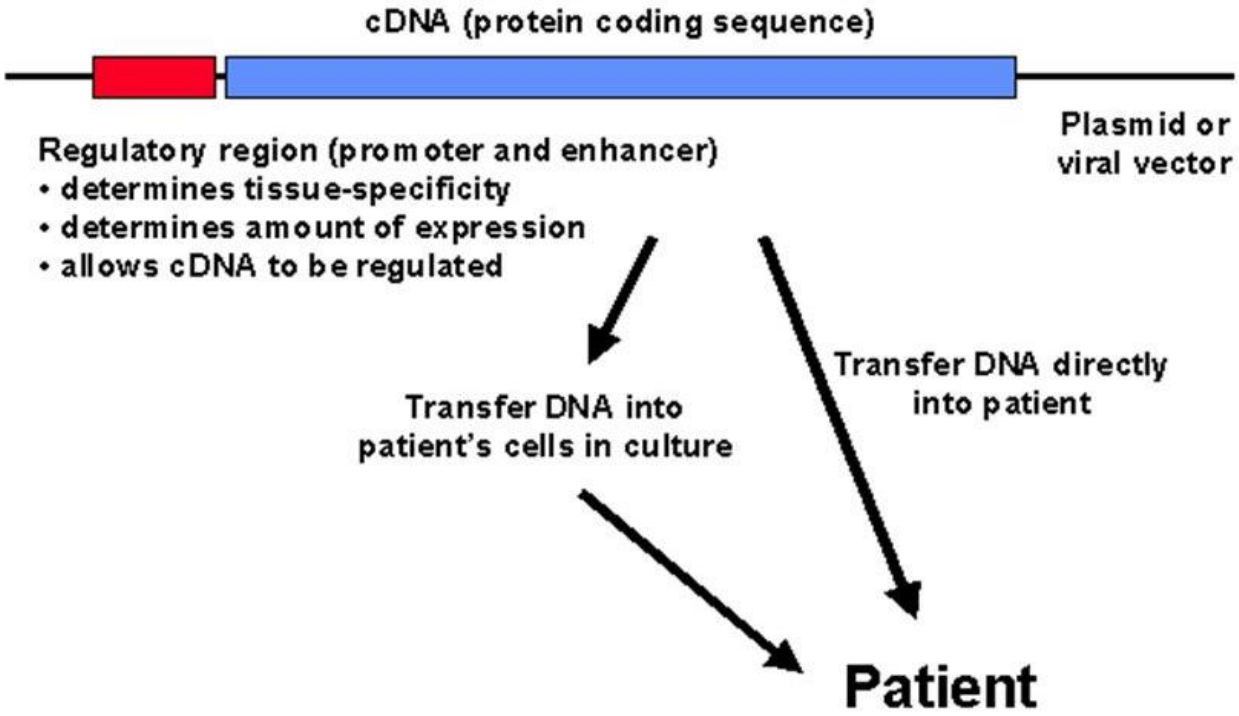
Gene therapy can be described as the intracellular delivery of genetic material to generate a therapeutic effect by correcting an existing abnormality or providing cells with a new function.

The process of Gene therapy

Viral vector takes a gene to the cell and places in the nucleus



Strategy for transfer of a gene to a patient



Germline vs Somatic gene therapy

Inherited or acquired disease

Cure(permanent) or treatment(temporary)

Risk/side effects(long term and short term)

Ethically acceptable or not

Potential of Gene Based therapeutics

Recent advances in the molecular and cellular biology of gene transfer have made it likely that gene therapy will soon start to play an increasing role in clinical practice.

It will not be restricted to the management of monogenic disorders, but will have applications across many other fields of medicine, particularly the treatment of cancer and infectious disease.

Prof. Sir David Weatherall FRs

Somatic gene therapy

Ex vivo delivery

In situ delivery

In vivo delivery

Ex vivo-cells removed, genetically modified, transplanted back into patient.

In situ- at the site of tissue damage

In vivo- direct transfer of genetic material into patient

Viral systems for gene delivery

Retroviral vectors

Adenoviral vectors

Adeno-associated viral vectors

Herpes simplex viral vectors

And several others

Ideal vector characteristics

Insert size: one or more genes

Targeted: limited to a specific cell type

No immune response

Stable: Not mutated

Production: easy to produce high concentrations(titer)

Regulatable: produce enough protein to cause an effect

Non-Viral gene delivery systems

Lipid-mediated delivery system e.g. cationic liposomes

Cationic polymer based systems

Naked DNA e.g. wit nanoparticles using a gene gun

Peptide based vectors

Hybrid systems

Non-Viral DNA carriers

Cationic liposomes: positively charged lipids interact with negatively charged DNA(lipid-DNA).
Transverse cell membrane

Advantages:

a. Stable complex
b. Can carry large size DNA
c. Can target to specific cells
d. Does not induce immunological reactions.

Disadvantages

a. Low transfection efficiency
b. Transient expression.
c. Inhibition by serum
d. Some cell toxicity

Non-Viral vectors

1. ***Liposomes***
2. ***Cationic polymers***
3. ***Naked DNA***
4. ***Peptide mediated***
5. ***Hybrid system***

May overcome limitations with viruses including small capacity for therapeutic DNA. Difficulty in cell type targeting and safety concerns.

Summary of commonly used vectors

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Candidate diseases for application of gene therapy

Monogenic disorders

Multifactorial disorders

Cancers

Infectious disease

Monogenic disorders for GT

SCID due to ADA

Cystic fibrosis(CFTR, cystic fibrosis transmembrane conductance regulator)

Beta-globin disorders (thalassemia, sickle cell anemia)'

Hemophilia

Familial hypercholesterolemia

Gauchers disease

Genetic Defects that are Candidates for Gene Therapy

Disease	Defect	Incidence	Target Cells
Severe combined immunodeficiency (SCID)	Adenosine deaminase (ADA) in 25% of SCID patients	Rare	Bone-marrow cells or T lymphocytes
Hemophilia A	Factor VII deficiency	1:10,000 males	Liver, muscle, fibroblasts or bone marrow cells
Hemophilia B	Factor IX deficiency	1:30,000 males	
Familial hypercholesterolemia	Deficiency of low-density lipoprotein (LDL) raeceptor	1:1 million	Liver
Cystic fibrosis	Faulty transport of salt in lung epithelium	1:3000 Caucasians	Airways in the lungs
Hemoglobinopathies thalassemias	(Structural) defects in the α or β globin gene	1:600 in certain ethnic groups	
Gaucher's disease	Defect in the enzyme glucocerebrosidase	1:450 in Ashkenazi Jews	Bone marrow cells, macrophages
α_1 antitrypsin deficiency inherited emphysema	Lack of α_1 antitrypsin	1:3500	Lung or liver cells
Duchenne muscular distrophy	Lack of dystrophin	1:3000 males	Muscle cells

1990s
1st Successful gene therapy protocol
(William Anderson, Michael Blasie, and Ken Culver)

Treatment of ADA cause server immune deficiency. Recessive disease that results in the buildup of waste products that kill T cells.

Gene Therapy Successes

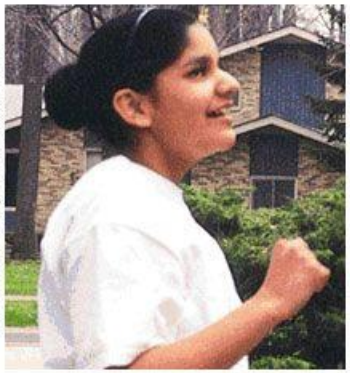

Photo courtesy of Van de Silva

Ashanti de Silva successfully treated for ADA deficiency - 1990

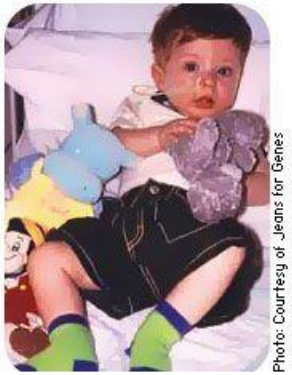

Photo: Courtesy of Jeans for Genes

Ryes Evans successfully treated for SCID - 2001

Genetic Science Learning Center

Gene therapy- An apparent success

Restenosis– reblockage of coronary arteries after they have been opened by coronary bypass surgery or angioplasty

13 patients with restenosis were injected in the heart with DNA encoding vascular endothelial growth factor, which promotes angiogenesis.

All 13 patients has improved heart function

Main problems in GT

Virus only infects a small number of cells.

The immune attacks the virus

Lose expression over time

Can have life threatening immune reaction

Gene therapy problems

Two boys treated for SCID developed leukemia due to disruption of a gene that regulates cell divison

Jesse Gelsinger died of complications due to an immunse system response while participating in a clinical trial.

Gene therapy– A Failure

Inability to produce ornithine transcarbamylase(OTC) is often lethal, but moderate deficiencies may be controlled by strict control of diet.

Jesse Gelsinger, a young volunteer in a gene therapy trial who has a moderate OTC deficiency , died on 17 Sept 1999.

He had bee injected in the liver with high concentrations of adenovirus that expressed OTC.

He apparently died of massive immune response to the adenovirus vector.

Gene therapy– Advantages

1. It has the ability to replace defective cells.

2. It promises a great untapped potential.

3. **It can help eradicate diseases.**

Gene therapy– Disadvantages

1. It can damage the gene pool.

2. It would modify human capabilities.

***3. I*t has the potential to give rise other disorders.**