आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

IFTM University, Moradabad, Uttar Pradesh

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IFTM University, Moradabad

GENE THERAPY

Prepared By:
Mr. Ashwin Saxena
School of Pharmaceutical Sciences,
IFTM University, Moradabad

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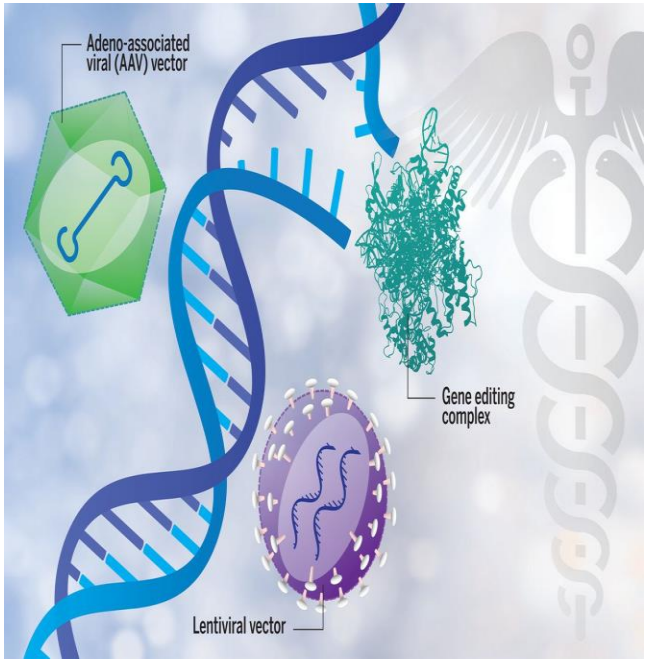
INTRODUCTION

WHAT IS GENE THERAPY?

- Gene therapy can be defined as an experimental technique for correcting defective genes that are responsible for disease development.
- The most common form of gene therapy involves inserting a normal gene to replace an abnormal gene.
- The first approved gene therapy experiment occurred on september 14,1990 in US,when Ashanti DeSilva was treated for ADA-SCID.



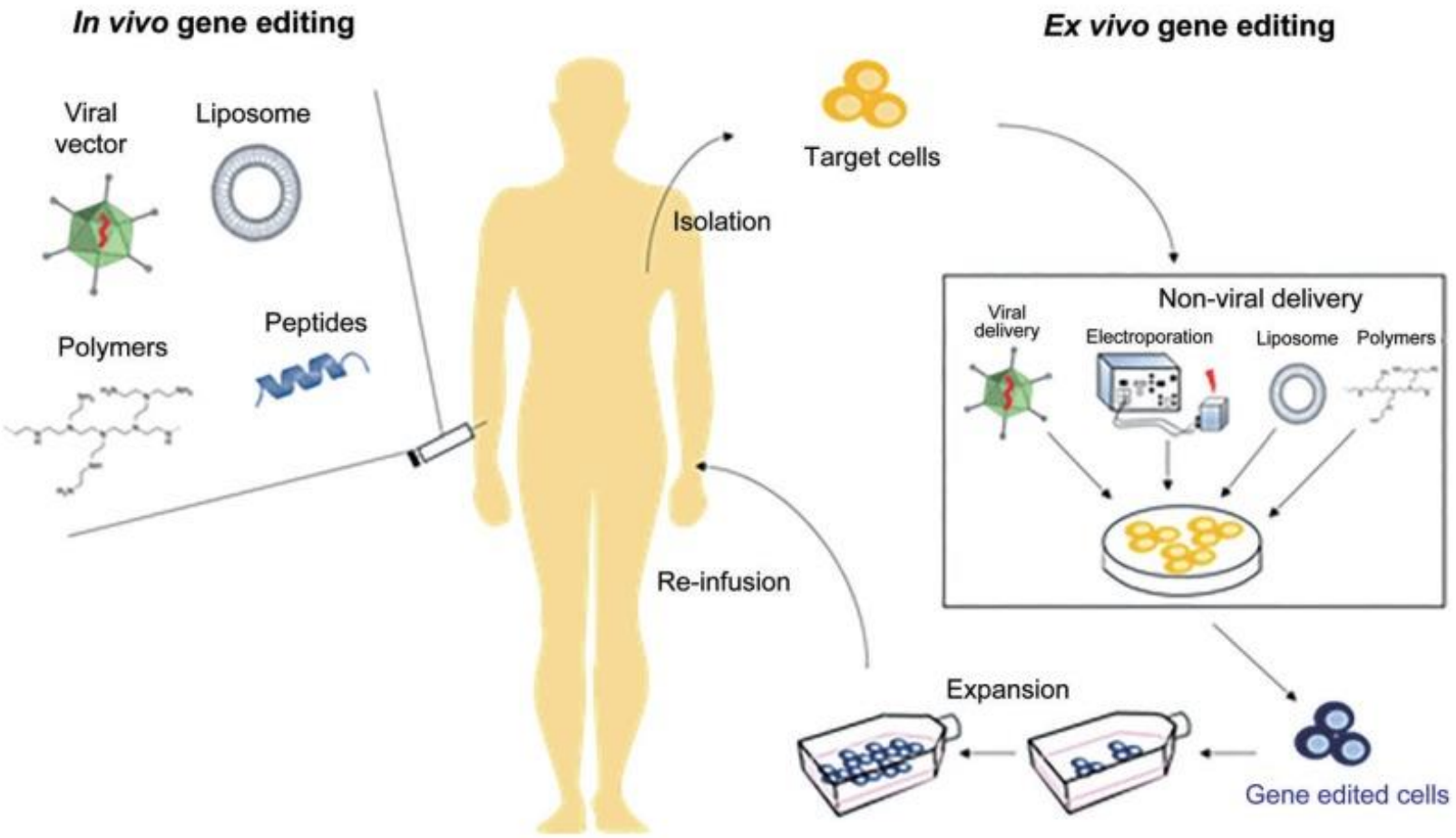
TYPES OF GENE THERAPY

SOMATIC CELL GENE THERAPY	GERM LINE GENE THERAPY
•Therapeutic genes transferred into the somatic cells	•Therapeutic genes transferred into the germ cells
Eg. Introduction of genes into bone marrow cells, blood cells, skin cells etc.	Eg. Genes introduced into eggs and sperms
•Will not be inherited later generations.	•It is heritable and passed on to later generations.
•At present all researches directed to correct genetic defects in somatic cells.	•For safety, ethical and technical reasons, it is not being attempted at present.

APPROACHES IN GENE THERAPY

- **IN VIVO GENE THERAPY:** Direct delivery of genes into the cells of a particular tissue in the body.
- **EX VIVO GENE THERAPY**: Transfer of genes to cultured cells and reinsertion.

APPROACHES IN GENE THERAPY…..



EX VIVO GENE THERAPY

- STEPS:

1. Isolate cells with genetic defects from a patient
2. Grow the cells in culture
3. Introduce the therapeutic genes
4. Select genetically corrected cells and grow.
5. Transplant the modified cells to the patient.

EXAMPLE OF EX VIVO GENE THERAPY

- 1st gene therapy: to correct deficiency of enzyme, Adenosine deaminase(ADA)
- Performed on a 4 yr old girl
- She was suffering from SCID- Severe combined immunodeficiency
- Caused due to defect in gene coding for ADA.

IN VIVO GENE THERAPY

- Direct delivery of the therapeutic gene into target cell into patients body.
- Carried out by viral and non viral vector systems
- It can be only possible option in patients where individual cells cannot be cultured in vitro in sufficient numbers.(eg-brain cells.)

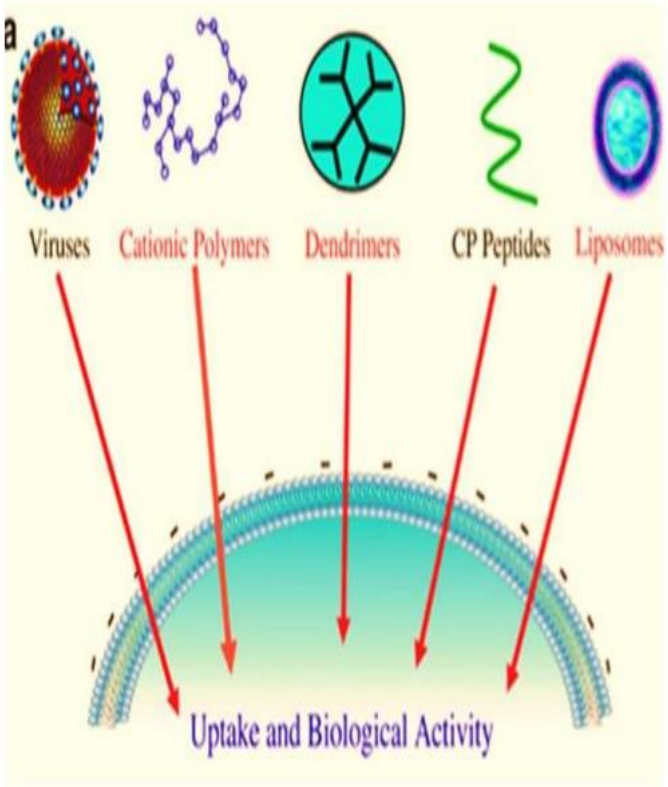
EXAMPLE OF IN VIVO GENE THERAPY

- Therapy for cystic fibrosis -
- In patients with cystic fibrosis, a protein called cystic fibrosis transmembrane regulator(CFTR) is absent.
- In the absence of CFTR chloride ions concentrate within the cells and it draws water from surrounding.
- This leads to the accumulation of sticky mucous in respiratory tract and lungs.
- Treated by in vivo replacement of defective gene by adenovirus vector.

VECTORS FOR GENE THERAPY

- To transfer the desired gene into a target cell, a carrier is required. Such vehicles of gene delivery are known as vectors.

- **Two main classes**
- Viral vectors
- Non viral vectors



VIRAL VECTORS

- 1) **retrovirus vector system**
- the recombinant retrovirus have the ability tointegrate into the host genome is a stable fashion.
- Target cell-dividing.

- 2**) adeno virus vector system-**
- Adeno virus with a DNA genome – good vector
- Target- non dividing human cell.

VIRAL VECTORS….

- 3**) Adeno associated virus vector-**It is a single stranded, non pathogenic small DNA virus.
- AAV enters host cell, becomes double stranded and gets integrated into chromosome.
- **4)Herpex simplex virus vector-**
- Viruses which have natural tendency to infect a particular type of cell.

NON VIRAL VECTORS

- **1)PURE DNA CONSTRUCT**
- Direct introduction of pure DNA construct into target tissue.
- Efficiency of DNA uptake by cells and expression rather low.
- Consequently Large quantities of DNA have to be injected periodically.
- **2) LIPOPLEXES**
- Liquid DNA complexes;DNA construct surrounded by artificial lipid layer.

NON VIRAL VECTORS….

- **3) DNA MOLECULAR CONJUGATES**
- Commonly used synthetic conjugates is poly-L- lysine bound to specific target cell receptor.
- Therapeutic DNA is then made to combine with the conjugate to form a complex.
- It avoids lisosomal breakdown of DNA.
- **4) HUMAN ARTIFICIAL CHROMOSOME:**
- Can carry a large DNA ie, with one or more therapeutic genes with regulatory elements.

METHODS OF GENE DELIVERY
PHYSICAL METHODS

- **GENE GUN**
- Employs a high- pressure delivery system to shoot tissue with gold or tungsten particles that are coated with DNA
- **MICRO INJECTION**
- Process of using a glass micropipette to insert microscopic substances into a single living cell.
- Normally performed under a specialized optical microscope setup called a micromanipulator.

CHEMICAL METHODS

- **USING DETERGENT MIXTURES**
- Certain charged chemical compounds like calcium phosphates are mixed with functional CDNA of desired function.
- The mixture is introduced near the vicinity of recipient cells
- The chemical disturbs the cell membrane, widens the pore size and allows the CDNA to pass through the cell.

CHEMICAL METHODS….

- **LIPOFECTION**
- It is a technique used to inject genetic materials into a cell by means of liposomes.
- Liposomes are artificial phospholipid vesicles used to deliver a variety of molecules including DNA into the cells.

OTHER TYPE OF GENE THERAPY

GENE AUGMENTATION THERAPY

- Most common form of gene therapy.
- Foreign gene replaces missing or defective gene.
- eg- replacement of defective p53 gene by a normal one in liver cancer
- **GENE INHIBITION THERAPY-**
- Done to block the over production of some proteins.
- 2 types- antigene and antisense therapy

ADVANTAGES

- Gene therapy has the potential to eliminate and prevent hereditary disease such as cystic fibrosis, ADA- SCID etc.
- It is a possible cure for heart disease, AIDS and cancer.
- It gives someone born with a genetic disease a chance to life.
- It can be used to eradicate diseases from the future generations.

DISADVANTAGES

- Long lasting therapy is not achieved by gene therapy; due to rapid dividing of cells benefits of gene therapy is short lived.
- Immune response to the transferred gene stimulates a potential risk to gene therapy.
- Viruses used as vectors for gene transfer may cause toxicity, immune responses, and inflammatory reactions in the host.
- Disorders caused by defects in multiple genes cannot be treated effectively using gene therapy.

ETHICAL ISSUES

- Who will have access to therapy?
- Is it interfering with God's plan?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence etc.
- Is it alright to use the therapy in the prenatal stage of development in babies?

CONCLUSION

- Theoretically, gene therapy is the permanent solution for genetic diseases.
- But it has several complexities. At its current stage, it is not accessible to most people due to its huge cost.
- A breakthrough may come anytime and a day may come when almost every disease will have agene therapy.
- gene therapy have the potential to revolutionize the practice of medicine.

RECENT DEVELOPMENTS

- In a new gene therapy method developed by University of Florida in Jan 2012, researchers found **treatment for a common form of blindness** that strikes both youngsters and adults.
- A gene therapy called **NLX-P101** dramatically reduces movement impairment in parkinson's patients. According to results of a phase 2 study published on March,2011 in the journal *Lancet Neurology.*

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