BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
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Programme: M.Sc., Biomedical Science
(5 Year Integrated Program)

Course Title : Principles of Genetics
Course Code : BM24C4

Unit-V
Gene Therapy and Ethical Issues

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Gene Therapy and Ethical Issues in Medical Genetics

(Carrier Testing, Population Screening, Probability Theory, and Risk Calculations)

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Gene Therapy

Gene therapy is a technique that modifies or replaces faulty genes to treat or prevent diseases.

Purpose:

Treat genetic disorders.

Provide long-term therapeutic effects.

Examples of **Treatable Disorders:**

Monogenic Disorders : Sickle cell anemia, hemophilia.

Complex Disorders : Cancer, cardiovascular diseases.

Types of Gene Therapy

1. **Ex-vivo Gene Therapy**

   Genes are altered outside the body in a laboratory and then transplanted back into the patient.

   Procedure:

   1.Harvest cells from the patient (e.g., stem cells).
   2.Modify the genetic material in the laboratory (e.g., add a functional gene).
   3.Reintroduce the genetically modified cells into the patient.

   Applications:

   SCID (Severe Combined Immunodeficiency): Correcting mutations in immune cells.
   Sickle Cell Disease: Editing hematopoietic stem cells to produce normal hemoglobin.

2. **In-vivo Gene Therapy**

   Genes are directly introduced into the patient's body using delivery vectors.

   Procedure:

   Vectors (viral or non-viral) deliver therapeutic gene directly to target tissues or cells.

   Applications:

   Leber Congenital Amaurosis: Direct delivery of the RPE65 gene to retinal cells.
   Cystic Fibrosis: Delivery of the CFTR gene to lung epithelial cells.

Gene Delivery Systems

Viral Delivery Systems

Viruses are modified to carry therapeutic genes without causing disease.

Types:

1. **Adenoviruses**:
   - •Efficient at delivering genes to a wide range of cells.
   - •Short-lived expression; potential immune response.
   - •Example: Used in cancer therapies.

2. **Adeno-Associated Viruses (AAV)**:
   - •High safety profile and long-term expression.
   - •Example: Used in spinal muscular atrophy treatment (*Zolgensma*).

3. **Retroviruses**:
   - •Integrate into the host genome, enabling stable expression.
   - •Example: Used in SCID treatments.

Non-Viral Delivery Systems

Physical or chemical methods to introduce DNA or RNA into cells.

Methods:

1. **Liposomes**: Lipid nanoparticles encapsulate genetic material for delivery to cells.
   mRNA vaccines (e.g., COVID-19).

2. **Electroporation**:
   Uses electric fields to make cell membranes permeable for gene entry.

3. **Direct Injection**: Naked DNA or RNA injected into tissues (e.g., muscle).

Comparison:

Feature	Viral Systems	Non-Viral Systems
Efficiency	High	Moderate
Safety	Moderate (immune risks)	High
Gene Expression	Stable	Temporary

Challenges in Gene Therapy

1. **Immune Response**:

   Viral vectors can trigger immune reactions, reducing effectiveness.

   Example: In early gene therapy trials, immune rejection led to complications.

2. **Off-Target Effects**:

   Genes may integrate into unintended sites in the genome, causing mutations or cancer

3. **Delivery Efficiency**:

   Difficulty in targeting specific tissues or organs.

4. **Cost and Accessibility**:

   High costs make gene therapy inaccessible to many.

   Example: *Zolgensma* costs over $2 million per treatment

Ethical Issues in Medical Genetics

Informed Consent

- Patients must fully understand the risks, benefits, and limitations of gene therapy.
- Example: Patients in gene therapy trials may face unforeseen risks.

Germline vs. Somatic Therapy

Somatic Therapy: Modifies genes in non-reproductive cells; changes are not inherited.
Example: Treating hemophilia in an individual.

Germline Therapy: Alters genes in eggs, sperm, or embryos, affecting future generations.

- **Ethical Concerns**: Risk of designer babies, unforeseen generational effects.
  Example: CRISPR editing in embryos has sparked global debate.

Equity and Access

Gene therapies are expensive and limited to developed countries.

Ethical Issue: Is it fair that only wealthy individuals or nations benefit?

Genetic Privacy

- Risk of genetic information misuse by employers or insurance companies.
- Example: Ethical concerns regarding genetic data sharing by companies like 23 and Me.

Safety Concerns

- Long-term effects of genetic modifications are unknown.
- Example:
  Jesse Gelsinger’s case (1999): Death during a gene therapy trial raised safety issues.

Human Enhancement

- Risk of using gene therapy for non-therapeutic purposes, such as enhancing intelligence or physical traits.

Applications of Gene Therapy

Condition	Therapeutic Gene/Vectors	Status
SCID	Retroviral vectors	Approved therapy
Leber Congenital Amaurosis	AAV vectors delivering RPE65 gene	Approved (Luxturna)
Sickle Cell Anemia	Gene editing using CRISPR-Cas9	Experimental trials ongoing
Hemophilia	AAV-mediated clotting factor genes	FDA-approved therapies available

Case Study: Spinal Muscular Atrophy (SMA)

Therapy Name : Zolgensma.
Mechanism : AAV vector delivers functional SMN1 gene to replace defective gene.
Outcome : Restores motor function and prevents early death.
Ethical Issues : High cost limits accessibility for many patients globally.

- Gene therapy offers revolutionary treatment options for genetic disorders.
- Ex-vivo and in-vivo methods cater to different therapeutic needs.
- Viral and non-viral delivery systems have unique advantages and challenges.
- Ethical issues, including safety, equity, and germline editing, remain critical concerns.