Gene Therapy (II)

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Objectives of this lecture

By the end of this lecture you will be able to:

1. Describe the different strategies for gene therapy
2. Select the suitable strategy based on the clinical case
3. Understand the complexity of clinical application of gene therapy
4. Evaluate proposed strategies according to the therapeutic need

Gene Therapy Strategies

- **Replacement of a missing or defective gene**
- **Introduction of gene(s) to influence cellular process**
- **Interference with gene products**

Replacement strategy

- Applies to diseases caused by single gene defects
- Transfer of a functional copy of the defective or missing gene
- Examples: enzyme deficiencies

Replacement strategy

- To apply this strategy, three requirements must be met:
  1. The specific gene defect must be known
  2. A functional copy of the gene must be available
  3. Target cells must be available and amenable to transfection methods resulting in long-term expression

Replacement strategy

Gene with defect	Disease/Disorder
Adenosine deaminase (ADA)	SCID
α-1-antitrypsin	Emphysema
CF transmembrane regulator	Cystic fibrosis
Clotting factor VIII	Hemophilia A
Clotting factor IX	Hemophilia B
β-chain of hemoglobin	Sickle cell anemia

Bubble Boy

David Phillip Vetter (September 21, 1971 – February 22, 1984)

Gene therapy trial

- First clinical trial in gene therapy was initiated in September 14, 1990
- Hematopoietic stem cells were isolated from the patient (4 y/o girl) and transduced with retroviral vector containing ADA gene
- 25% recovery of normal ADA in patient T cells

Why was ADA suitable?

- Single gene defect
- Gene was isolated and cloned in 1983
- HSC are easy to obtain and maintain *in vitro*

Influence strategy

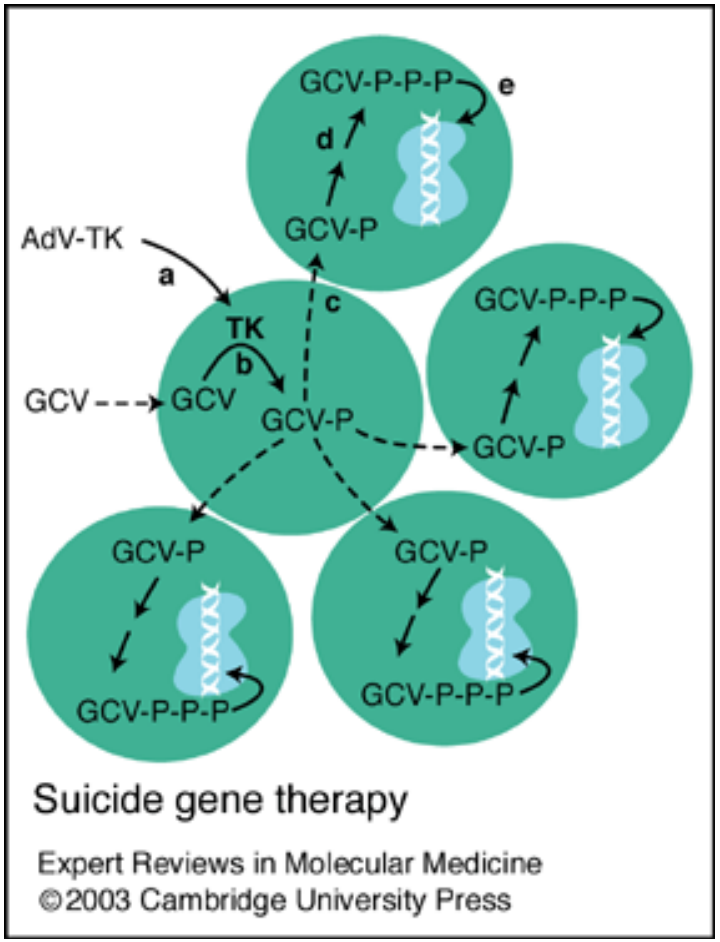
- Applies to complex disorders were more than one gene is involved
- Based on *in vitro* cloning of human genes that were derived from human tissue
- Examples: cancer

Areas of investigation

- Enhancement of anti-tumor response
- Introduction of drug-resistance genes
- Introduction of drug-sensitivity genes
- Replacement of tumor suppressor genes

Introduction of drug-sensitivity genes

- Suicide gene therapy
- Gene that converts non-toxic prodrug into a toxic metabolite
- Bystander effect
- Gancyclovir triphosphate
- Problem: it can transfect normal cells too



Now you are able to:

- ✓ Describe the different strategies for gene therapy
- ✓ Select the suitable strategy based on the clinical case
- ✓ Understand the complexity of clinical application of gene therapy
- ✓ Evaluate proposed strategies according to the therapeutic need