Gene therapy

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Gene therapy

- Gene therapy involves the direct genetic modification of the cells of a person (or animal disease model) in order to achieve a therapeutic goal. The genetic modification involves the transfer of some artificial genetic construct,
- It is an approach to treat, cure, or ultimately prevent disease by changing the expression of a person's genes.
- Gene therapy involves the direct genetic modifications of the cells of the patients in order to achieve a therapeutic goal.
- The transferred genetic material may be-

  (i)Gene,

  (ii)Gene segment,

  (iii)Oigonuceotides

Gene therapy for SCID

The first successfu gene therapy was carried out On September 14, 1990 of a Severe Combined Immunodeficiency disease (SCID) patient named Ashanti desilva.

Gene altered cells were delivered in to the blood stream of Ashanti desilva

Lack of adenosine deaminase leads to destruction of T-lymphocytes.

Gene for ADA production is located on chromosome no.20.

Fate of transferred gene

(1)Integrated gene-

transferred gene may be integrated in the host genome, the integration is random.

Advantages-

i. expression stable,

ii. long lasting,

iii. proper segregation during cell division

Disadvantages-

i. Random integration

ii. Insertion may occur in heterochromatic region

iii. Insertion may cause activation of oncogene

iv. Insertion may cause insertional inactivation of vital gene

(2) Non-integrated gene

transferred gene may present as episome in the nucleus of the host .

Advantages-

No risk of insertional activation or inactivation

Disadvantages-

On the basis of the target cells the gene therapy is broadly classified in to-

(i) Germ line gene therapy

-produces a permanent transmissible modification

-banned due to ethical reasons

(ii)Somatic cell gene therapy

modify the cells or tissues of the patients in a way that is confined to only that patients

According to the procedure , gene therapy is classified in to–

(i) *ex vivo* gene therapy

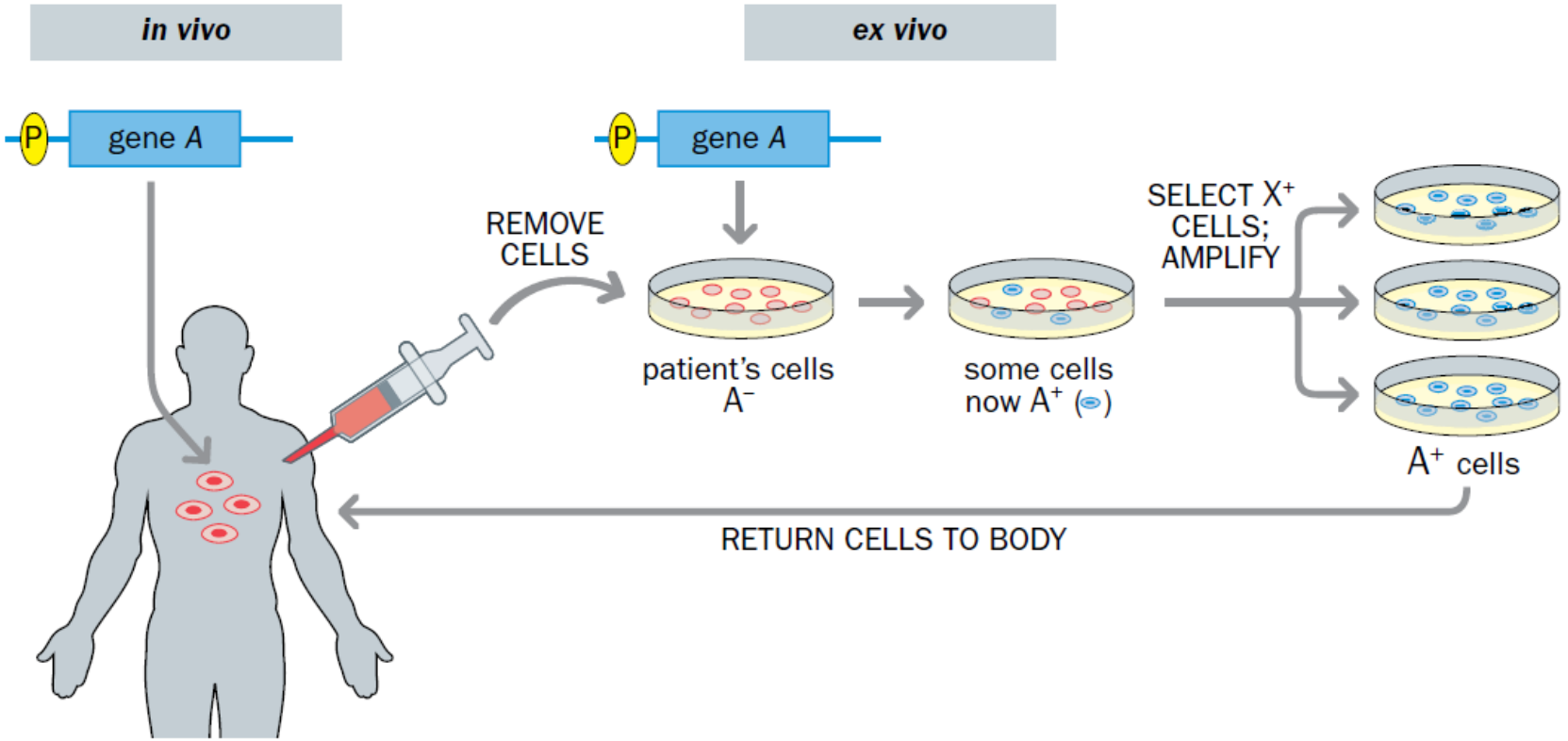
Affected cells removed , transformed with normal copy of gene and are returned to the patients body.

The cells are selected, amplified in culture, and returned to the patient.

(ii) *in vivo* gene therapy

vectors having therapeutic genes are directly placed in to affected organ/tissue/cells.

For many tissues ex vivo gene therapy is not possible, and the cells must be modified within the patient's body.



***Ex vivo and in vivo gene* therapy**

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Types of mutations

(i)Loss of function mutation

-recessive

-inactivation of gene/ lack of gene

(ii)Gain of function mutation

- dominant

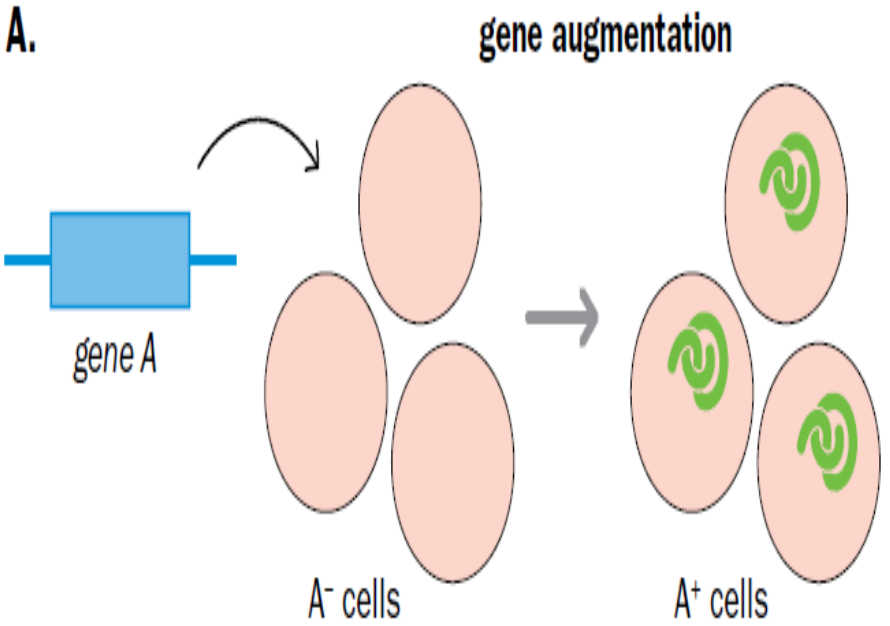
- acquire a new function

Approaches of somatic gene therapy

1. Gene supplementation therapy/ gene augmentation therapy
2. Targeted killing of specific cells/
3. Indirect killing of specific cells
4. Targeted gene mutation correction/Gene replacement
5. Targeted inhibition of gene expression

1. Gene supplementation therapy/ Gene augmentation therapy (GAT)

- Applied in monogenic disorders
- Introduce extra copy/copies of the normal gene
- Applied in autosomal recessive disorders
- Disorders in which loss of mutations occur in gene i. e. inactivation of gene
- **Examples-**
- In treatment of cystic fibrosis- introduction of normal copy of CFTR gene
- Normal copy of p53 gene in cancers



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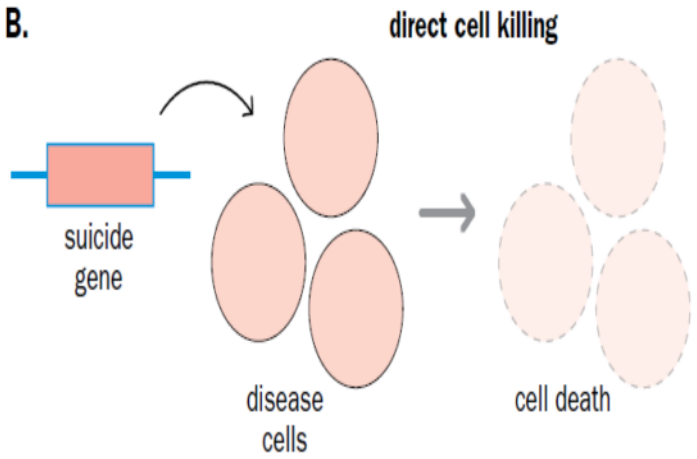
2.Targeted killing of specific cells/

- Mostly used in cancer gene therapy

(a)Lethal Toxin genes/suicide genes are transferred in to the target cells (e. g ricin, shigela toxin, diptheria toxin)

Or

(b)A gene encoding prodrug is transferred, conferring susceptibility to killing by a subsequently administered drug



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3. Indirect killing of specific cells

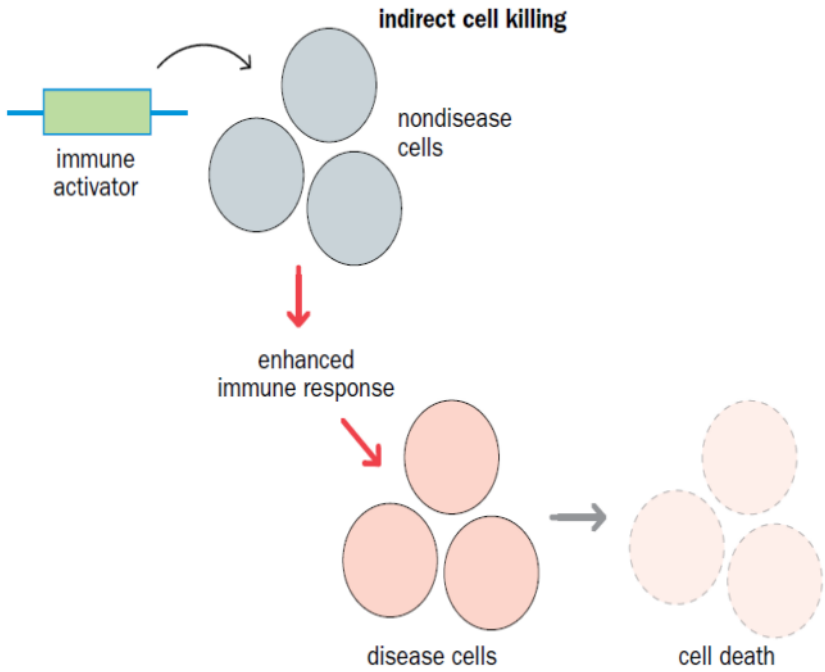
Mostly used in cancer gene therapy

Transfer immunostimulatory genes to enhance immune response for killing of specific cells.

(a)Delivery of foreign antigenic gene

(b)Delivery of foreign MHC genes

(c)Delivery of cytokine genes



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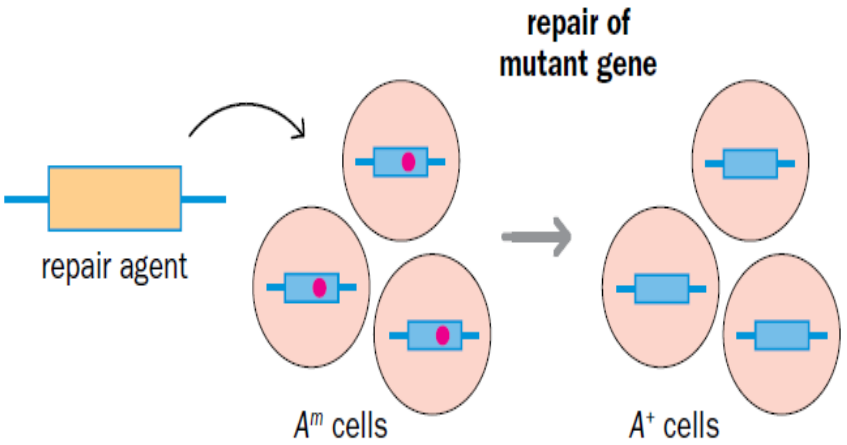
4. Targeted gene mutation correction/Gene replacement

- Used in gain of function mutation cases
- The mutation in pathogenic gene is corrected
- This approach is due to practical difficulties in not yet applied
- In principle, it can be done at gene level by homologous recombination.
- Example-
- Huntigtons disease



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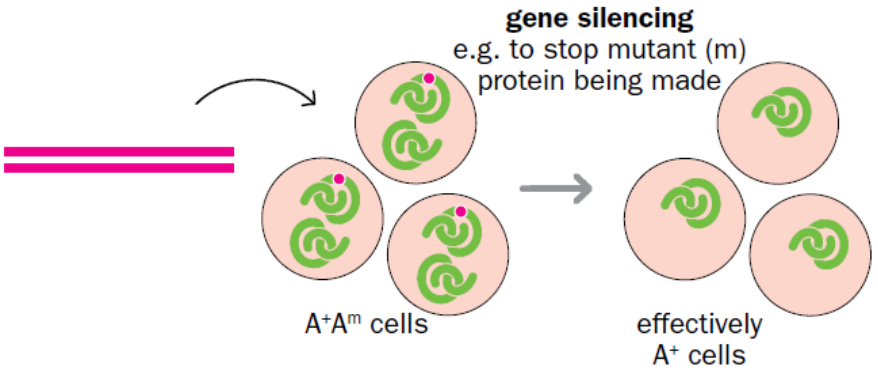
5.Targeted inhibition of gene expression

- Gain of function mutation
- Disease cells display a novel gene product or inappropriate expression of a gene



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