GENETIC SCREENING AND GENE THERAPY

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HISTORY

- Technology to detect and treat inborn diseases came up in 1961
- In 1990 first approved gene therapy case was reported in USA .
- In 1992 Dr. Claudio Bordignon, Milan, Italy performed the first procedure of gene therapy using hematopoietic stem cells
- In 2002 first successful gene therapy treatment for adenosine deaminase deficiency was reported

- In 2006- VRX-496 was the first gene based therapy for treatment of HIV was used.
- In 2007- Moorfields eye hospital and University College of London, Institute of Opthalmology announced the world's first gene therapy trial for Inherited Retinal Disease
- Till 2008 more than 1200 clinically applicable genetic tests were available.

WHAT IS GENETIC SCREENING?

- A technique used to determine genotype / phenotype of an organism
- Determines risk of having or passing the genetic disorder to next generation.
- Used to detect faulty or abnormal genes
- Can also detect genes related to an increased risk for cancer

GENETIC TESTING

- Based on analysis of chromosomes (DNA), proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutation, phenotypes, or karyotypes for clinical purpose.
- Involves:
  - Direct examination of DNA
  - DNA based tests
  - Biochemical tests for enzymes
  - Micoscopic examination of stained or fluorescent chromosomes

TYPES OF TESTS

- Cell free fetal DNA- A non invasive technique, performed by venous blood of mother and can provide information about fetus early in pregnancy e.g. Down's Syndrome
- New-born Screening- used just after the birth to identify genetic disorders which can be treated early in life e.g Phenylketonuria
- Diagnostic Screening- used to rule out a specific genetic or chromosomal condition e.g Polycystic Kidney Disease

CONT…

- Carrier testing- used to identify people who carry one copy of gene mutation (carrier). The testing is performed in individuals with family history of genetic disorders e.g. Cystic fibrosis
- Preimplantation genetic diagnosis- performed on human embryoes prior to the implantation as part of IVF.
- Prenatal Diagnosis- used to detect changes in fetal genes or chromosomes before birth. It is performed in early days of pregnancy and uses sample from mother's amniotic sac (amniosentesis).

CONTD....

- Predictive and presymtomatic testing- used to detect gene mutations associated with disorders that appear after birth, often later in life. Predictive testing can identify developing disorders e.g. Breast Cancer caused due to mutation in BRCA1 gene. Presymptomatic screening can determine whether a person will develop a genetic disorder e.g. Hemochromatosis.
- Pharmacogenomics- determines the influence of genetic variation for drug purpose

NON-DIAGNOSTIC TESTING

- Forensic testing- uses DNA sequences to identify an individual for legal purposes e.g. Used to identify crime or catastrophe victim.
- Paternal testing- uses special DNA markers to identify the same or similar inheritance patterns between related individuals.
- Genealogical DNA test- used to determine ancestry or ethnic heritage for genetic genealogy.
- Research testing- includes finding unknown genes

DISEASES FOR GENETIC SCREENING

- Adult Polycystic Kidney Disease
- Alpha-1-antitrypsin deficiency
- Alzheimer's Disease
- Ataxia telangiectasia
- Central Core Disease
- Cystic Fibrosis
- Fragile X- syndrome
- Emanuel syndrome
- Gaucher Disease
- Hereditary hemochromatosis
- Huntington's Disease
- Hemophilia A and B
- Marfan Syndrome
- Inherited breast and ovarian cancer
- Myotonic syndrome
- Phenylketonuria
- Polycystic Kidney Disease

INDICATIONS FOR PRENATAL DIAGNOSIS

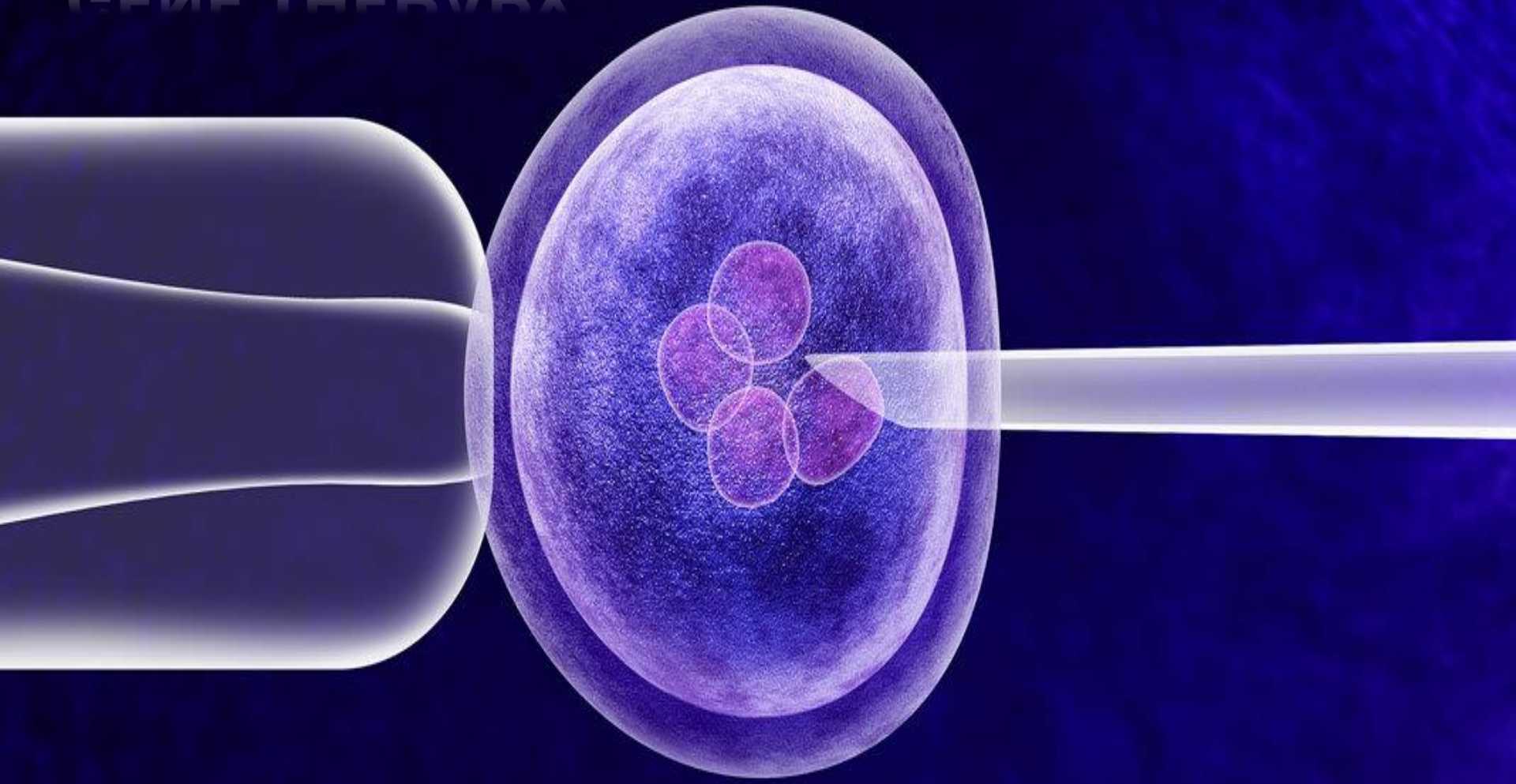
- Abnormal results in prenatal screening
- Any child with chromosome abnormality
- Probability of translocation carrier in parents
- Family history of chromosome abnormality
- Family history of a single gene disorder
- Family history of neural tube defect or other congenital abnormalities

PROS AND CONES OF GENE TESTING

- Timely diagnosis and physician consultation
- Timely termination of diseased pregnancy
- Delegation of information to people at high risk
- Transforming of fatal condition to a treatable one
- Possibility of laboratory errors
- Potential for provoking anxiety, risks for discrimination and social stigmatization


Genetic Screening
Counselling
Gene Therapy

GENE THERAPY



Introduction of functional genetic material into target cells to replace or supplement defective gene, or to modify the target cells tso as to achieve therappeutic goals

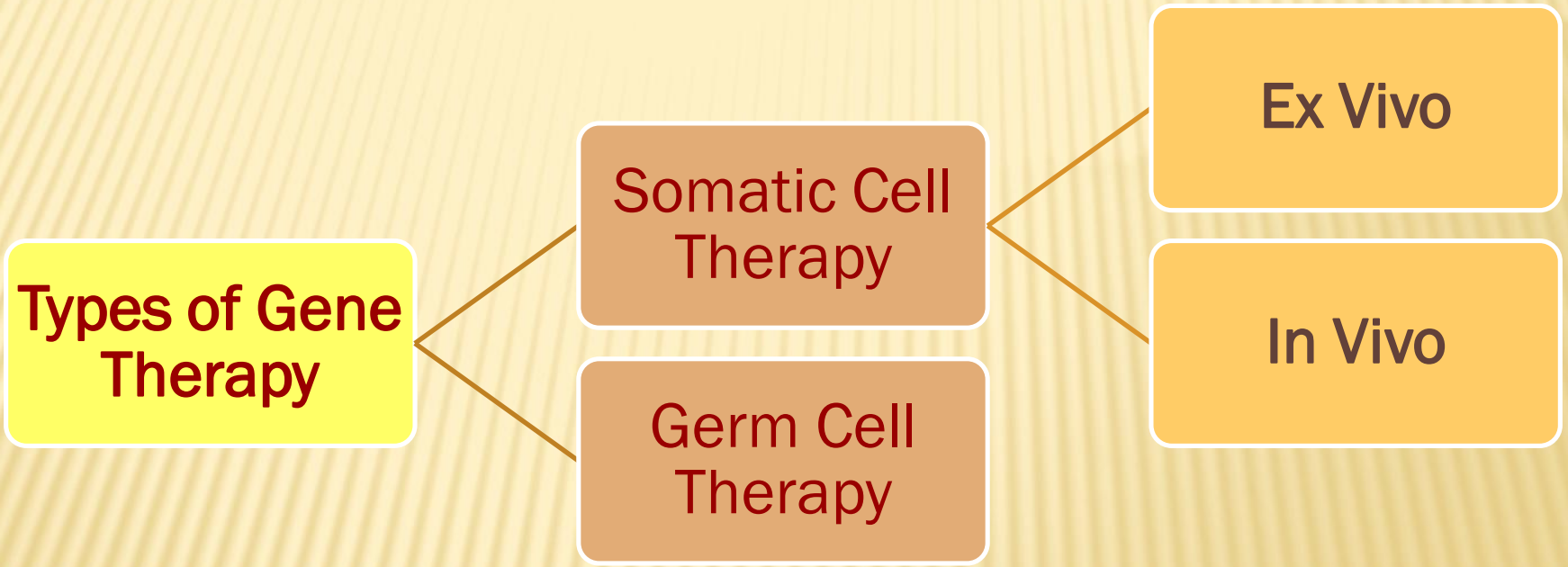
- Theoretically somatic cells as well as germ cells can be targeted
- However, practically only somatic cells are targeted
- Using germ cells arises controversies

Human genome is like a huge libarar

Completion of human genome project in 2003 has provided novel opportunities for gene therapy

APPROACHES

1. **Gene Replacement/Correction - Replacing a mutated gene with a healthy copy e.g Severe Combined Immunodeficiency**
2. **Gene Silencing/Gene Interference- Inactivating or "knocking out" a mutated gene e.g Sickle cell Disease**
3. **Gene Augmentation/ Gene Addition- Introducing a new gene to help fight disease e.g. Parkinson's Disease**
4. **Suicide gene- kills the cells by either apoptosis or makes cells vulnerable to drugs e.g. Solid tumors**


Types of Gene Therapy
Somatic Cell Therapy
Germ Cell Therapy
Ex Vivo
In Vivo

GERM LINE THERAPY

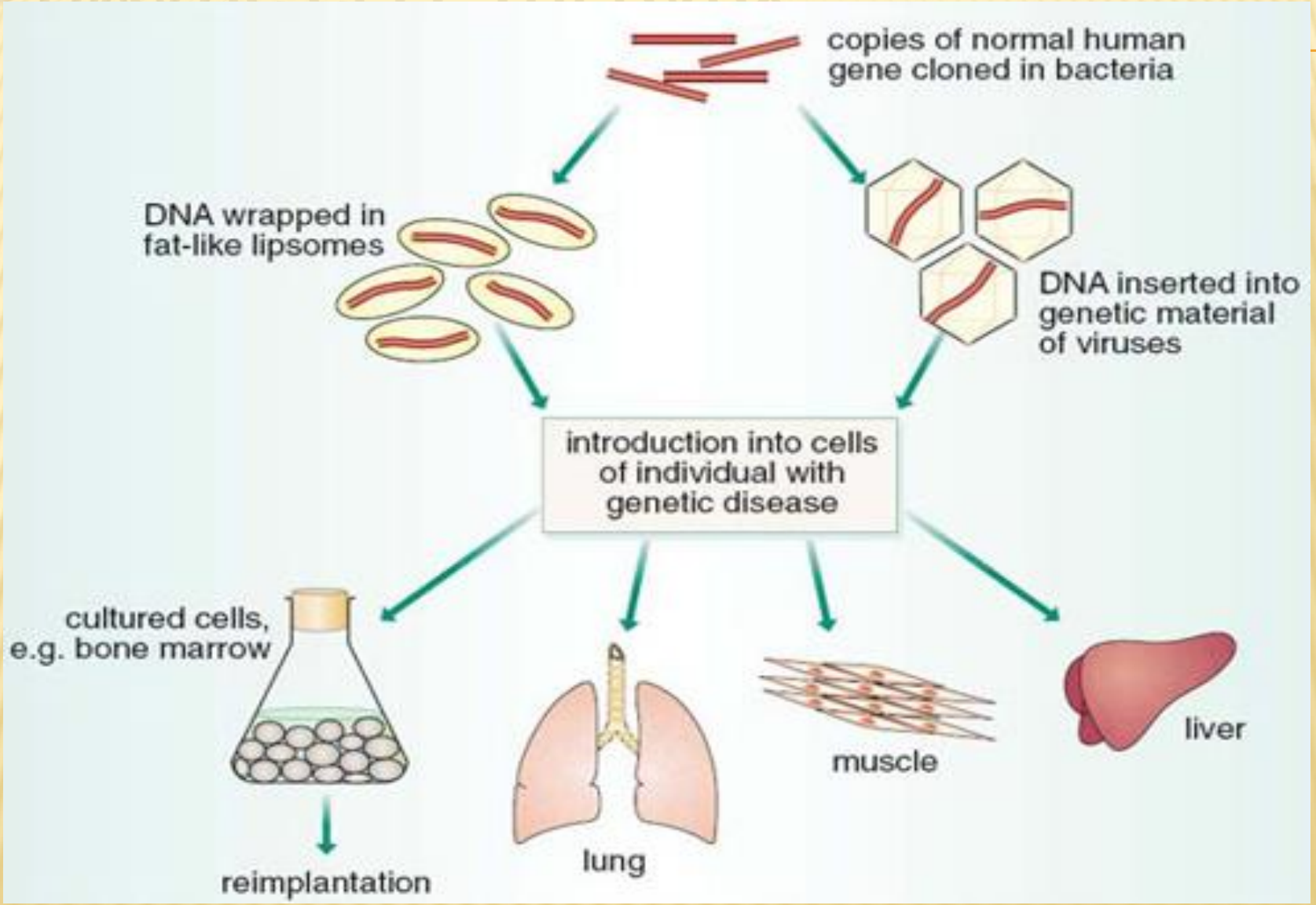
Altering the gene of an egg or sperm

Or

Altering of Blastomere during an early stage of its division

Considered to be unethical

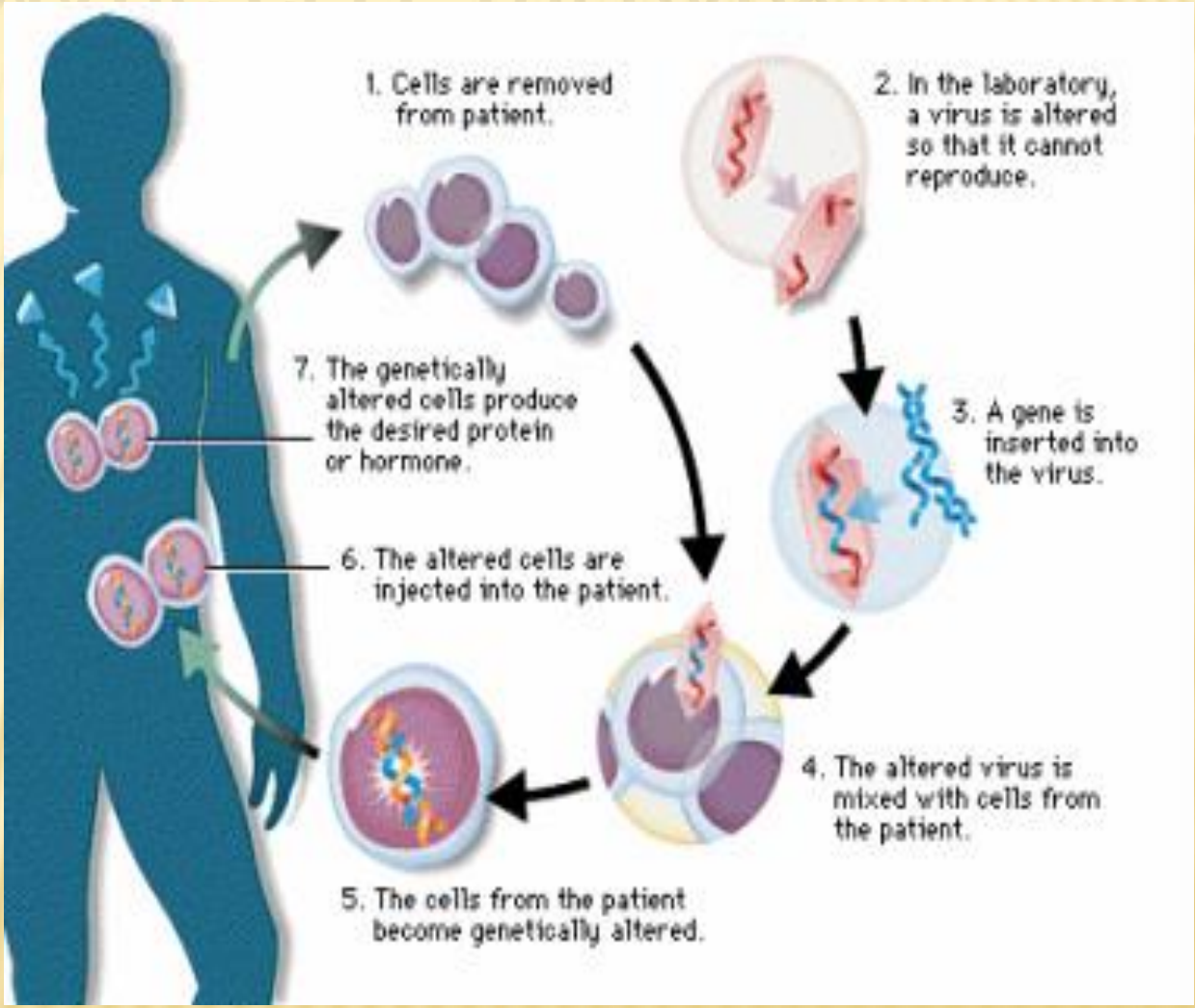
SOMATIC CELL THERAPY



https://www.open.edu/openlearn/science-maths-technology/science/biology/gene-therapy/content-section-3

EX VIVO SOMATIC CELL THERAPY

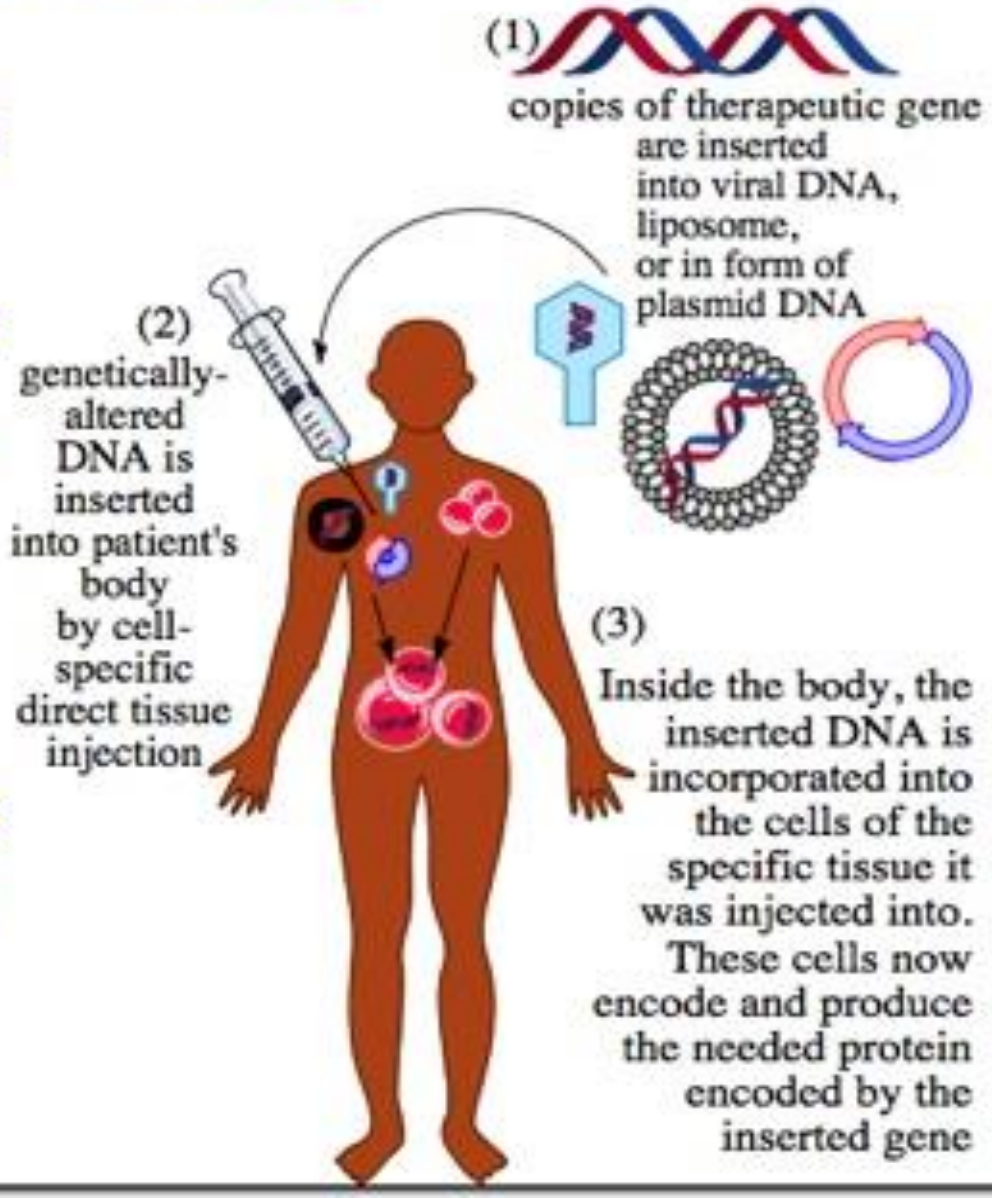
The cells are treated outside the human body in culture conditions



Source: Dorin, J. (1996). Somatic gene therapy. *British Medical Journal.* Retrieved from: http://search.proquest.com/docview/203970434?accountid=29001

In Vivo Gene Therapy

In vivo gene therapy involves introduction of therapeutic DNA directly into the patient's body. The DNA is introduced by cell-specific direct injection into tissue in need. DNA in the form of a plasmid vector is introduced by a dermal vaccination. Modified liposomes are not currently used for gene therapy, but they will likely be the next advancement in therapeutic gene delivery as cell-specific receptor-mediated DNA carriers. Once inside the body and in contact with the specifically targeted cells, the inserted DNA is incorporated into the tissue's cells where it encodes the production of the needed protein.

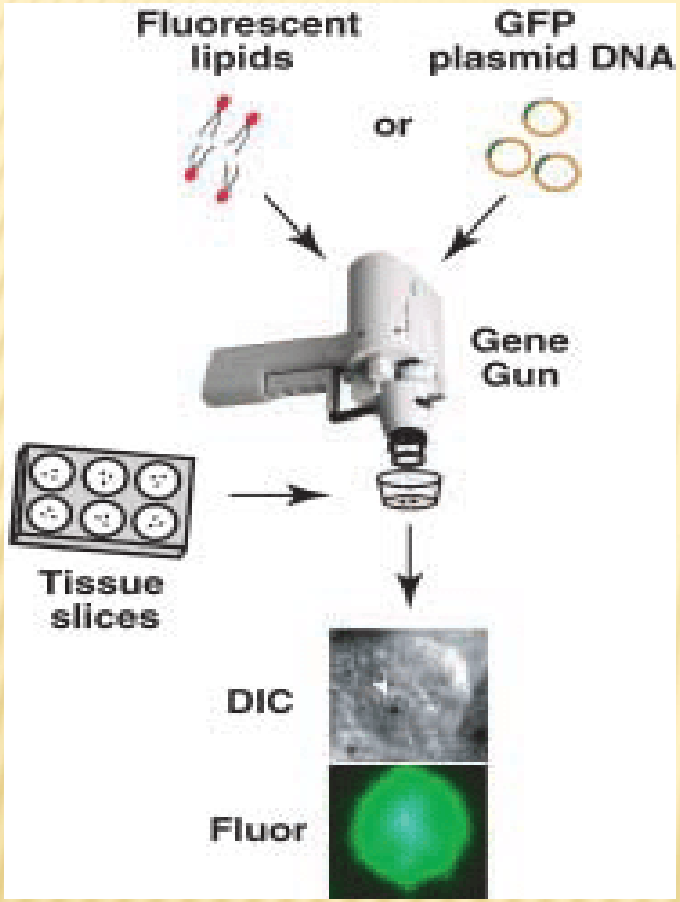


Source: 'In vivo gene therapy' By Lizanne Koch via Wikimedia

VECTORS FOR GENE THERAPY

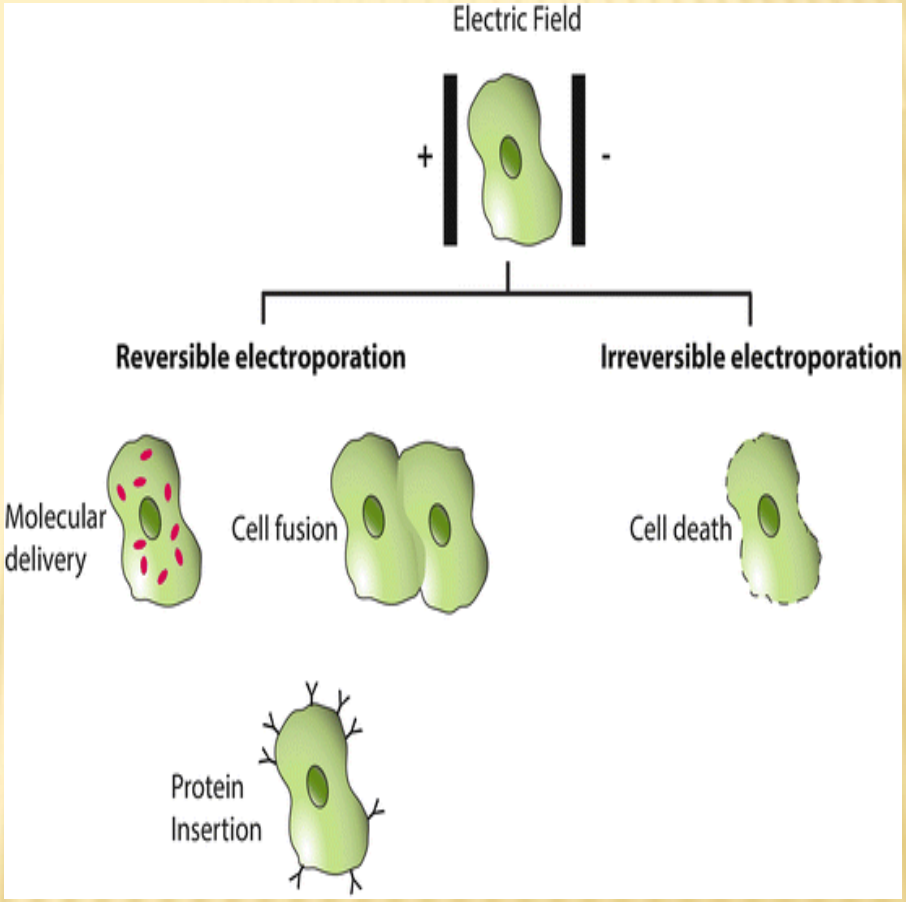
PHYSICAL	CHEMICAL	BIOLOGICAL
• Microinjection • Gene Gun • Sonoporation • Electroporation	• Oligonucleotides • Liposomes • Calcium Phosphate • Dendrimers	• Retrovirus • Adenovirus • HSV • Adeno associated viruses

PHYSICAL GENE THERAPY



GENE GUN

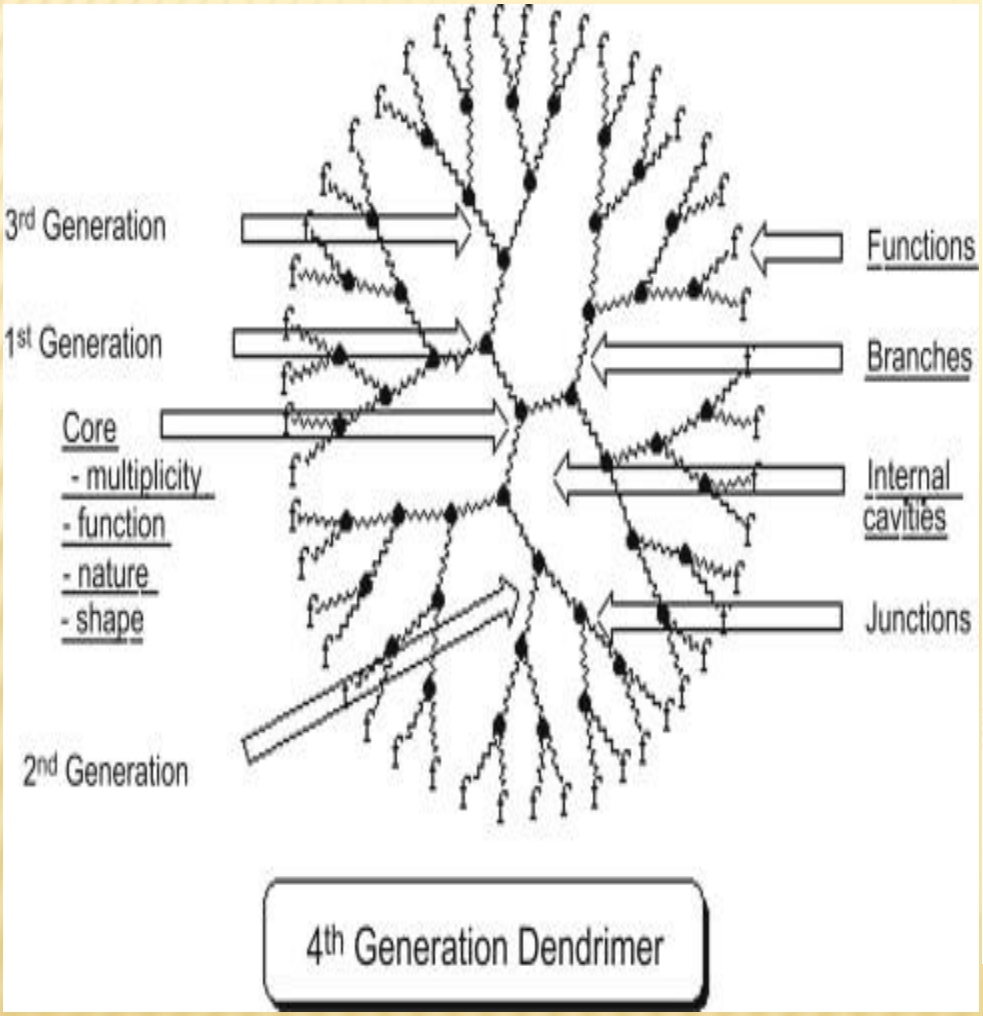
SOURCE: BRAIN MAPPING THE METHODS, JAN 2002



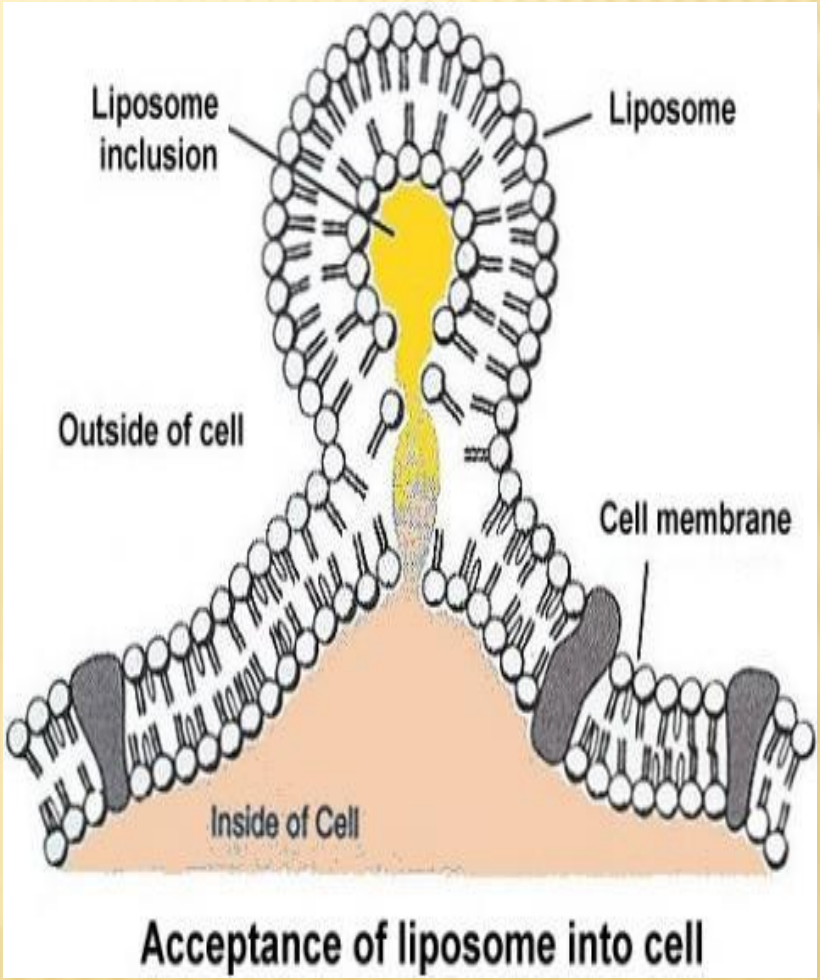
ELECTROPHORATION

SOURCE: HANDBOOK OF ELECTROPHORATION

CHEMICAL GENE THERAPY



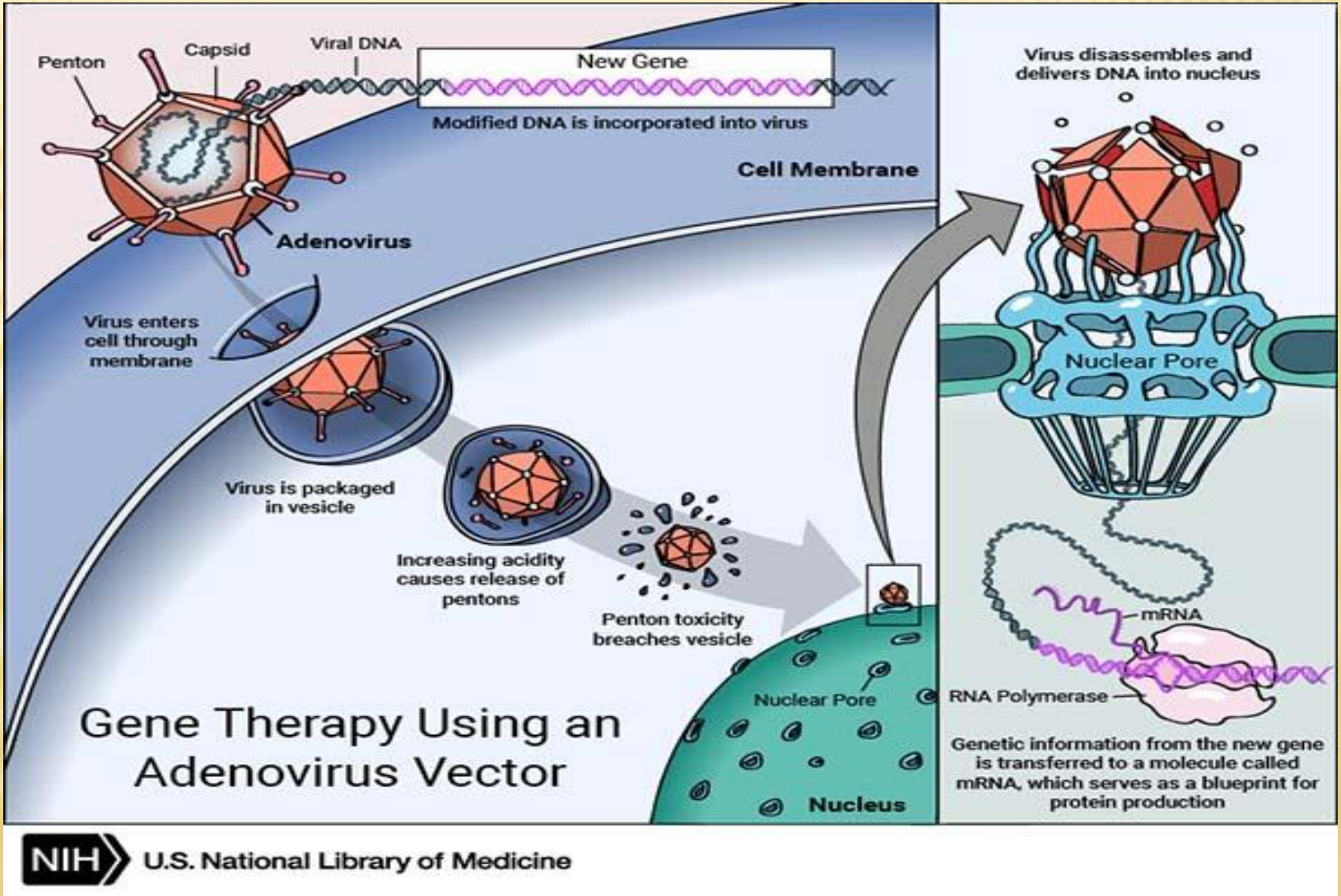
SOURCE: NANOTECHNOLOGY APPLICATIONS FOR TISSUE ENGINEERING,2015



LIPOSOMES

SOURCE: GENE THERAPY REVIEW

BIOLOGICAL GENE THERAPY



DRUGS IN MARKET FOR GENE THERAPY

- Gendicine- an adenovirus –p53 based gene
- Glybera- an adeno assocaited virus for familial lipoprotein lipase deficiency treatment
- Luxturna- an adeno virus associated treatment for retinal dystrophy
- Imlygic- genetically modified oncolytic virus
- Kymriah- Lentivirus for treatment of B-cell precursor acute lymphoblastic leukemia

- THANK YOU