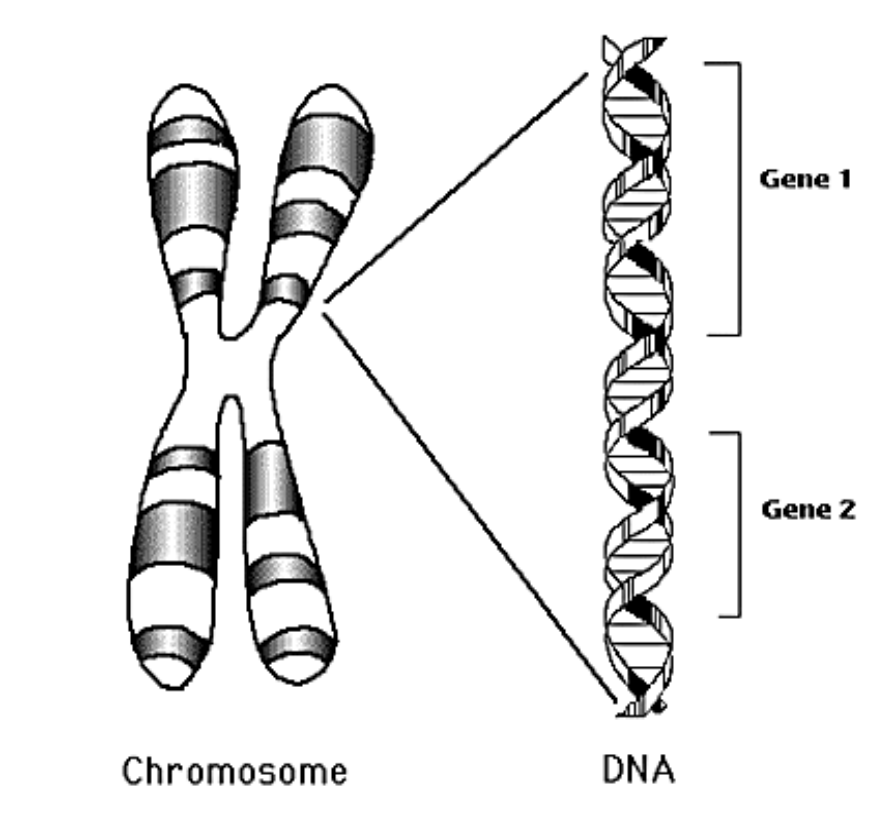
Gene Therapy


The Future of Medicine
Gene Therapy

- Are carried on a chromosome
- The basic unit of heredity **Genes**
- Encode how to make a protein
  - DNA→RNA →proteins
- Proteins carry out most of life's function.
- When altered causes dysfunction of a protein
- When there is a mutation in the gene, then it will change the codon, which will change which amino acid is called for which will change the conformation of the protein which will change the function of the protein. Genetic disorders result from mutations in the genome.

Picture of a Chromosome

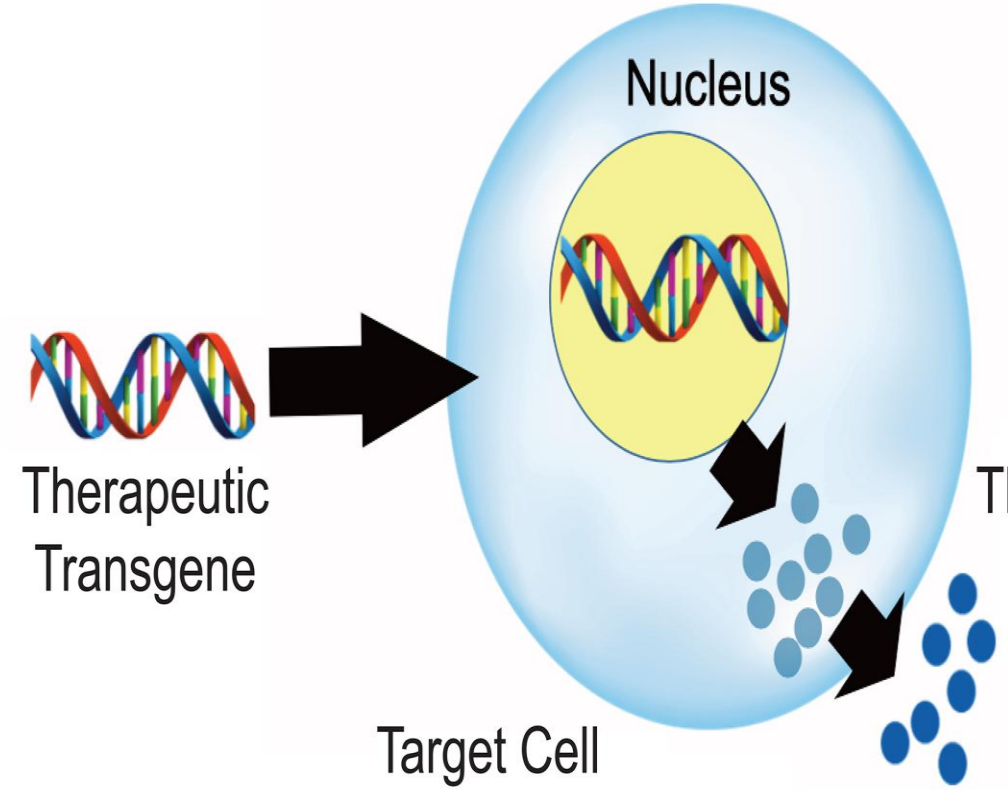


http://www.accessexcellence.org/RC/VL/GG/genes.html

What is Gene Therapy

- It is a technique for correcting defective genes that are responsible for disease development
- There are four approaches:
  1. A normal gene inserted to compensate for a nonfunctional gene.
  2. An abnormal gene traded for a normal gene
  3. An abnormal gene repaired through selective reverse mutation
  4. Change the regulation of gene pairs

The Principle of Gene Therapy



https://genetherapy.isth.org/getting-to-know-gene-therapy-terminology-and-concepts-interactive-module

The Beginning…

- In the 1980s, Scientists began to look into gene therapy.
  - They would insert human genes into a bacteria cell.
  - Then the bacteria cell would transcribe and translate the information into a protein
  - Then they would introduce the protein into human cells

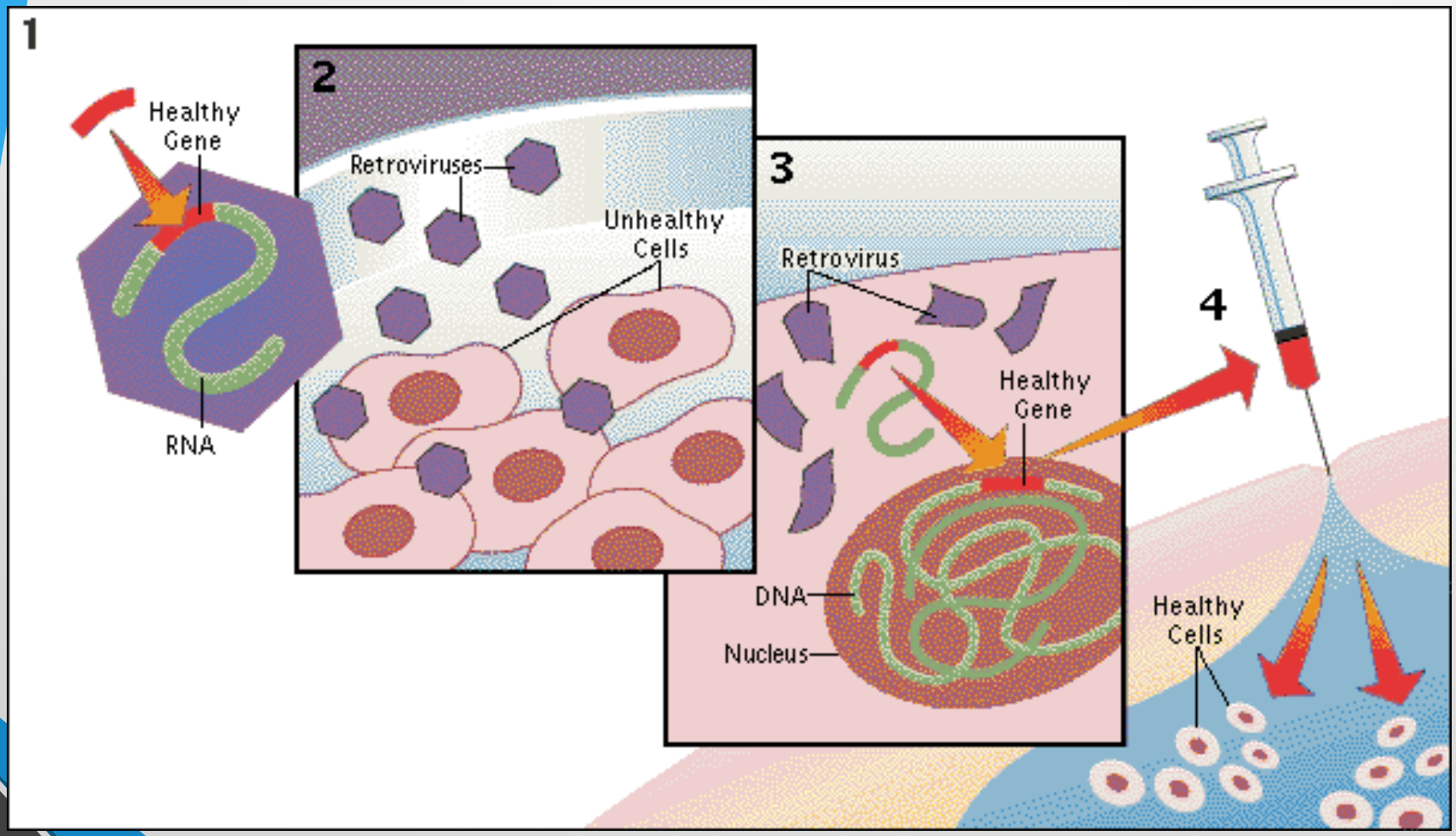
The First Case

- The first gene therapy was performed on September 14th, 1990
  - Ashanti DeSilva was treated for SCID
    - Sever combined immunodeficiency
  - Doctors removed her white blood cells, inserted the missing gene into the WBC, and then put them back into her blood stream.
  - This strengthened her immune system
  - Only worked for a few months ☹

How It Works

- A vector delivers the therapeutic gene into a patient's target cell
- The target cells become infected with the viral vector
- The vector's genetic material is inserted into the target cell
- Functional proteins are created from the therapeutic gene causing the cell to return to a normal state

Picture ☺



http://encarta.msn.com/media_461561269/Gene_Therapy.html

Viruses

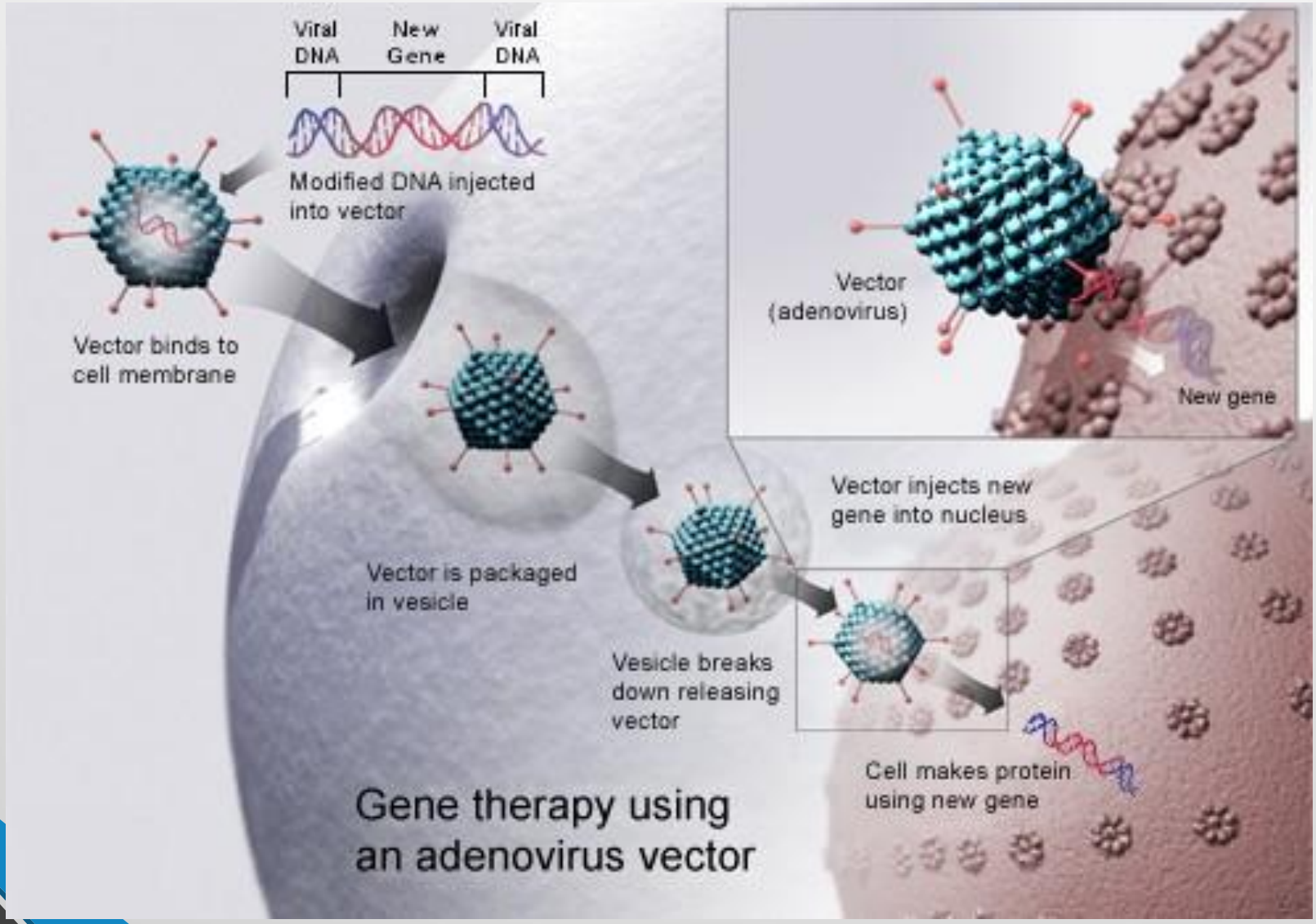
- Replicate by inserting their DNA into a host cell
- Gene therapy can use this to insert genes that encode for a desired protein to create the desired trait
- Four different types

Retroviruses

- Created double stranded DNA copies from RNA genome
  - The retrovirus goes through reverse transcription using reverse transcriptase and RNA
  - the double stranded viral genome integrates into the human genome using integrase
    - integrase inserts the gene anywhere because it has no specific site
    - May cause insertional mutagenesis
      - One gene disrupts another gene's code (disrupted cell division causes cancer from uncontrolled cell division)
  - vectors used are derived from the human immunodeficiency virus (HIV) and are being evaluated for safety

Adenoviruses

- Are double stranded DNA genome that cause respiratory, intestinal, and eye infections in humans
- The inserted DNA is not incorporate into genome
- Not replicated though ☹
  - Has to be reinserted when more cells divide
- Ex. Common cold



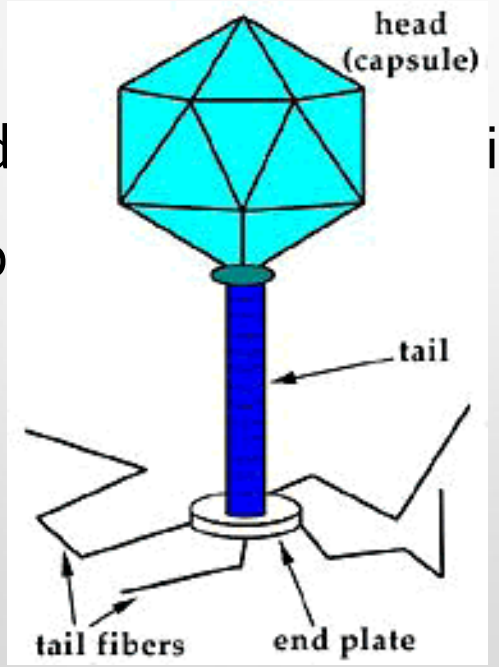
http://en.wikipedia.org/wiki/Gene_therapy

Adeno-associated Viruses

- Adeno-associated Virus- small, single stranded DNA that insert genetic material at a specific point on chromosome 19
- From parvovirus family- causes no known disease and doesn't trigger patient immune response.
- Low information capacity
- gene is always "on" so the protein is always being expressed, possibly even in instances when it isn't needed.
- hemophilia treatments, for example, a gene-carrying vector could be injected into a muscle, prompting the muscle cells to produce Factor IX and thus prevent bleeding.
    - Study by Wilson and Kathy High (University of Pennsylvania), patients have not needed Factor IX injections for more than a year

Herpes Simplex Viruses

- Double stranded infect neurons
- Ex. Herpes simp



http://www.ucmp.berkeley.edu/alllife/virus.html

Non-viral Options

- Direct introduction of therapeutic DNA
  - But only with certain tissue
  - Requires a lot of DNA
- Creation of artificial lipid sphere with aqueous core, liposome
  - Carries therapeutic DNA through membrane
- Chemically linking DNA to molecule that will bind to special cell receptors
  - DNA is engulfed by cell membrane
  - Less effective ☹
- Trying to introduce a 47th chromosome
  - Exist alongside the 46 others
  - Could carry a lot of information
  - But how to get the big molecule through membranes?

Current Status

- FDA hasn't approved any human gene therapy product for sale

Reasons:

- In 1999, 18-year-old Jesse Gelsinger died from multiple organ failure 4 days after treatment for omithine transcarboxylase deficiency.
  - Death was triggered by severe immune response to adenovirus carrier
- January 2003, halt to using retrovirus vectors in blood stem cells because children developed leukemia-like condition after successful treatment for X-linked severe combined immunodeficiency disease

Problems with Gene Therapy

- Short Lived
  - Hard to rapidly integrate therapeutic DNA into genome and rapidly dividing nature of cells prevent gene therapy from long time
  - Would have to have multiple rounds of therapy
- Immune Response
  - new things introduced leads to immune response
  - increased response when a repeat offender enters
- Viral Vectors
  - patient could have toxic, immune, inflammatory response
  - also may cause disease once inside
- Multigene Disorders
  - Heart disease, high blood pressure, Alzheimer's, arthritis and diabetes are hard to treat because you need to introduce more than one gene
- May induce a tumor if integrated in a tumor suppressor gene because insertional mutagenesis

Unsuccessful Gene therapies

- Jesse Gelsinger, a gene therapy patient who lacked ornithine transcarbamylase activity, died in 1999.
- Within hours after doctors shot the normal OTC gene attached to a therapeutic virus into his liver, Jesse developed a high fever. His immune system began raging out of control, his blood began clotting, ammonia levels climbed, his liver hemorrhaged and a flood of white blood cells shut down his lungs.
- One problem with gene therapy is that one does not have control over where the gene will be inserted into the genome. The location of a gene in the genome is of importance for the degree of expression of the gene and for the regulation of the gene (the so-called "position effect"), and thus the gene regulatory aspects are always uncertain after gene therapy

Successful Gene Therapy for Severe Combine Immunodeficiency

- Infants with severe combined immunodeficiency are unable to mount an adaptive immune response, because they have a profound deficiency of lymphocytes.

- severe combined immunodeficiency is inherited as an X-linked recessive disease, which for all practical purposes affects only boys. In the other half of the patients with severe combined immunodeficiency, the inheritance is autosomal recessive — and there are several abnormalities in the immune system when the defective gene is encoded on an autosome.

Severe Combine Immunodeficiency Continued

- A previous attempt at gene therapy for immunodeficiency was successful in children with severe combined immunodeficiency due to a deficiency of adenosine deaminase. In these patients, peripheral T cells were transduced with a vector bearing the gene for adenosine deaminase. The experiment was extremely labor intensive, because mature peripheral-blood T cells were modified rather than stem cells, and the procedure therefore had to be repeated many times to achieve success.

Successful One Year Gene Therapy Trial For Parkinson's Disease

- Neurologix a biotech company announced that they have successfully completed its landmark Phase I trial of gene therapy for Parkinson's Disease.

- This was a 12 patient study with four patients in each of three dose escalating cohorts. All procedures were performed under local anesthesia and all 12 patients were discharged from the hospital within 48 hours of the procedure, and followed for 12 months. Primary outcomes of the study design, safety and tolerability, were successfully met. There were no adverse events reported relating to the treatment.

Parkinson's Disease Cont.

- The gene transfer procedure utilized the AAV (adeno-associated virus) vector, a virus that has been used safely in a variety of clinical gene therapy trials, and the vehicle that will be used in all of the company's first generation products, including epilepsy and Huntington's disease. In its Parkinson's disease trial, Neurologix used its gene transfer technology.

Recent Developments

- Genes get into brain using liposomes coated in polymer call polyethylene glycol
  - potential for treating Parkinson's disease
- RNA interference or gene silencing to treat Huntington's
  - siRNAs used to degrade RNA of particular sequence
  - abnormal protein wont be produced
- Create tiny liposomes that can carry therapeutic DNA through pores of nuclear membrane
- Sickle cell successfully treated in mice

http://www.wellesley.edu/Biology/Courses/219/Gen_news/i3_Gene_Therapy.jpg

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