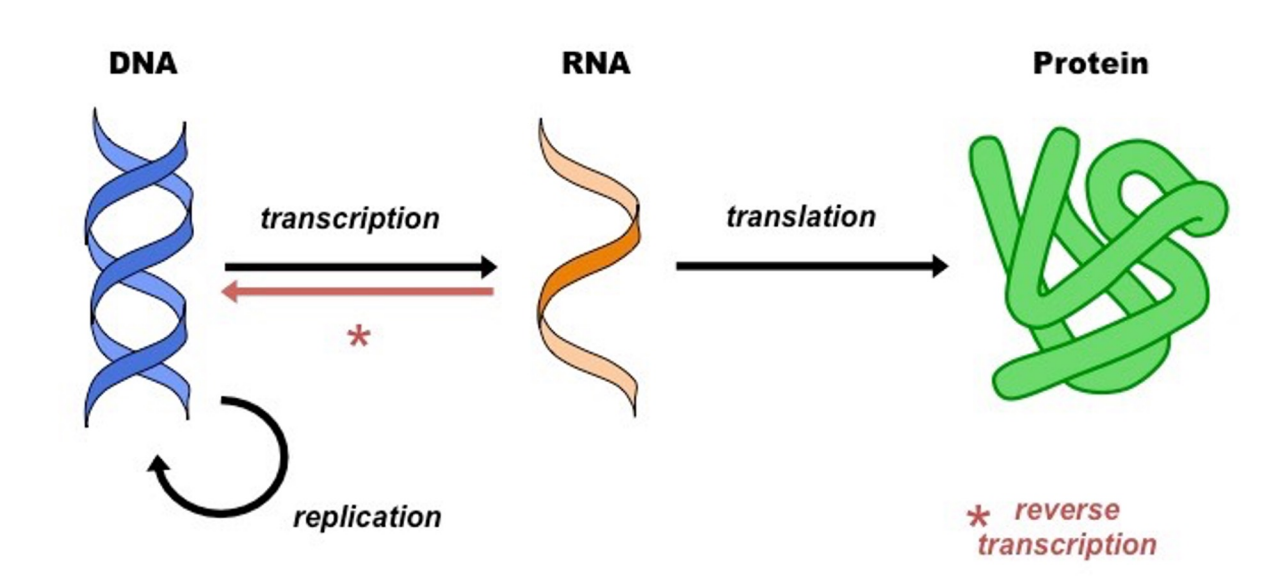
Introduction

- Conventional drug design vs. recombinant proteins vs. gene therapy
- Examples of genetic engineering
- Types of gene therapy

Central Dogma Molecular Biology



R-DNA

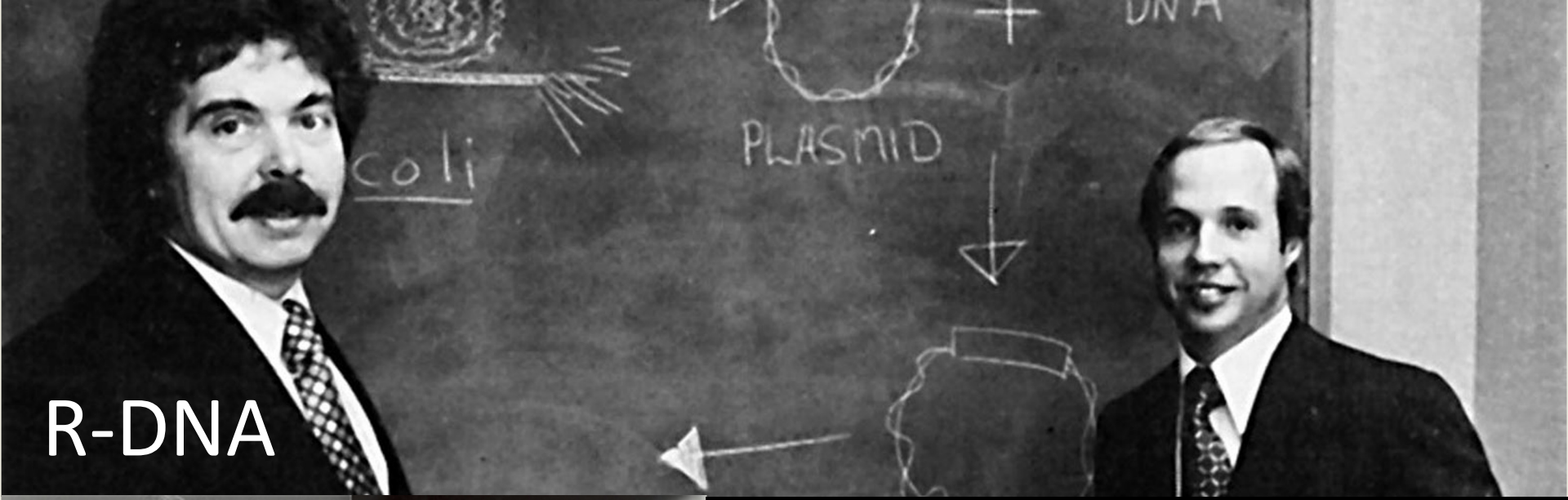


Photo courtesy of Herbert Boyer

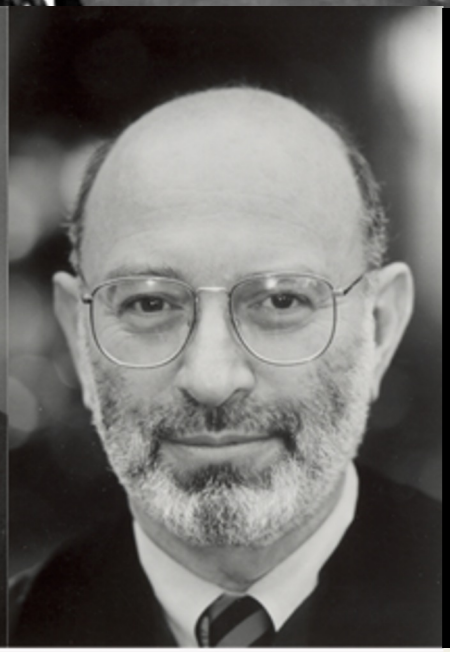
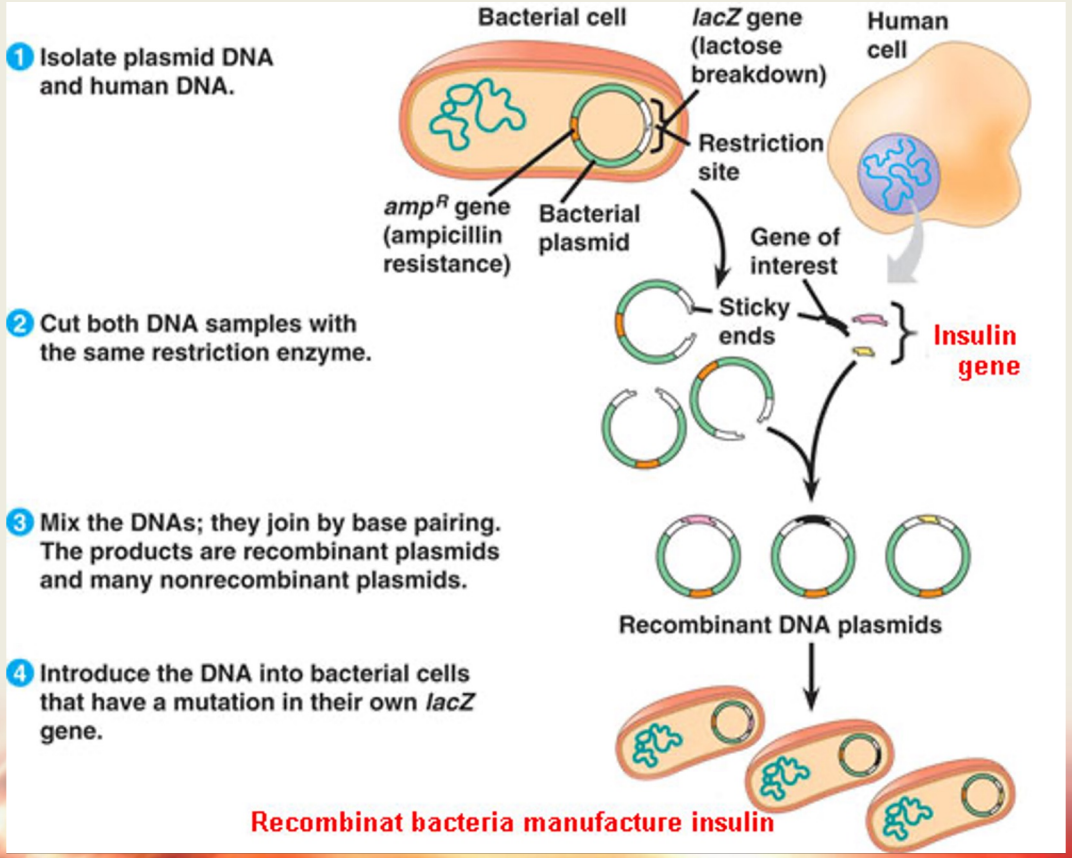


Photo courtesy of Stanford University

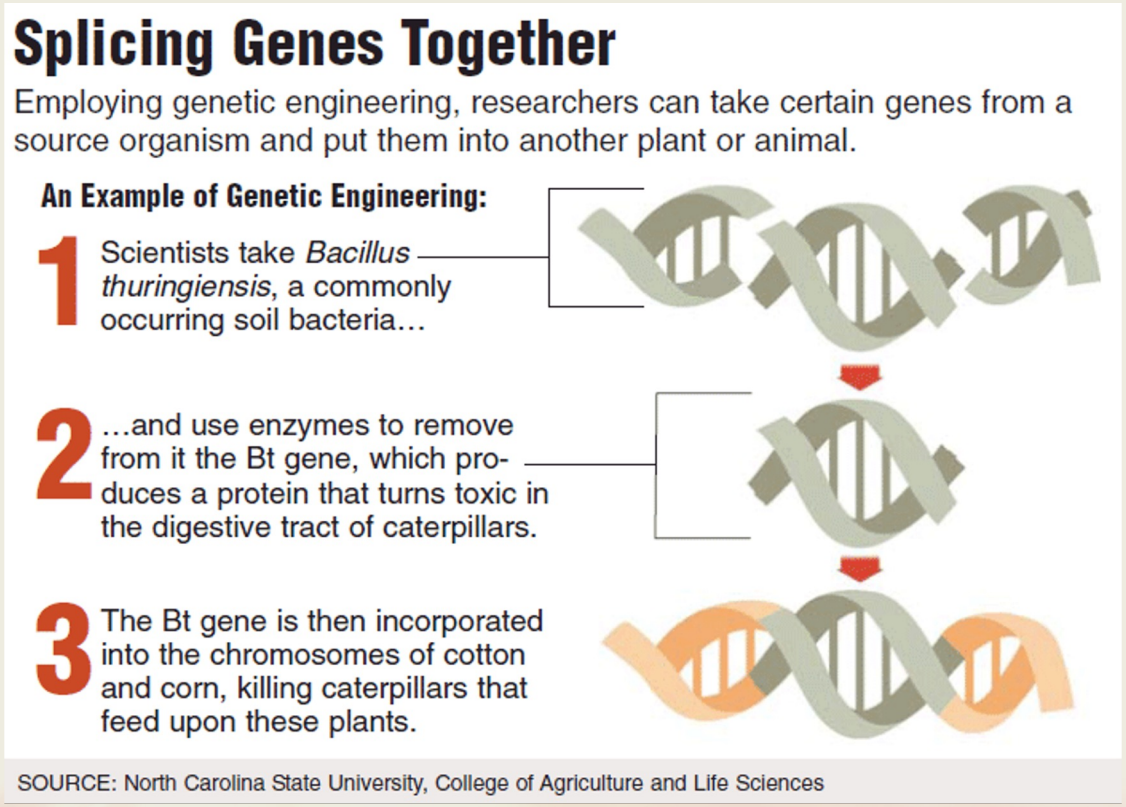
Successful Gene Modification

- Have used bacteria to produce desired products



Successful Gene Modification

- Modified plants to impart insecticides



Successful Gene Modification

- Modified DNA for aesthetic purposes

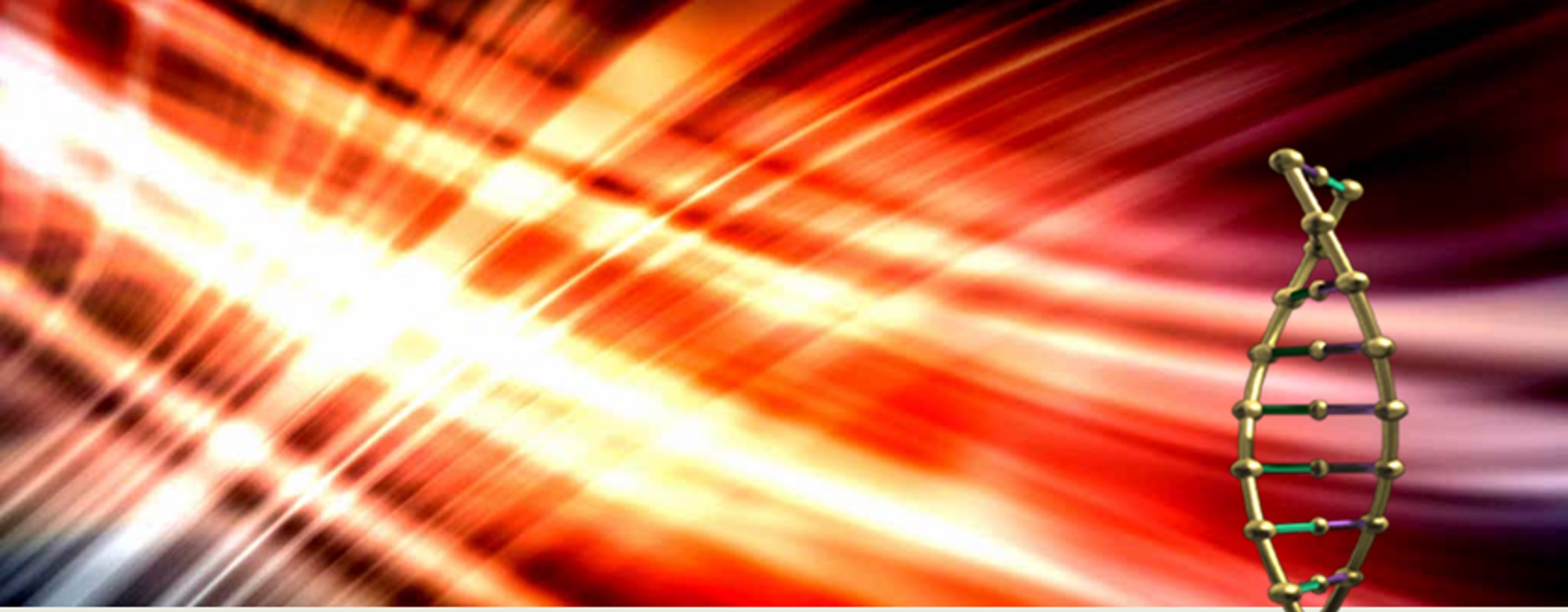
- The **GloFish®** is a brand of fluorescently colored genetically modified fish.

https://www.youtube.com/watch?v=kv5TlkAN3z8

Flavr Savr Tomato

- Genetically modified tomato
- 1st commercially grown genetically engineered food to be granted a license for human consumption.
- Produced by Californian company 'Calgene' submitted to U.S FDA in 1992
- It has increased storage life by suppression of polygalacturonase (PG) gene resulting transformation of antisence expression PG cDNA.

In Vivo Gene Therapy



A Different Kind of Approach

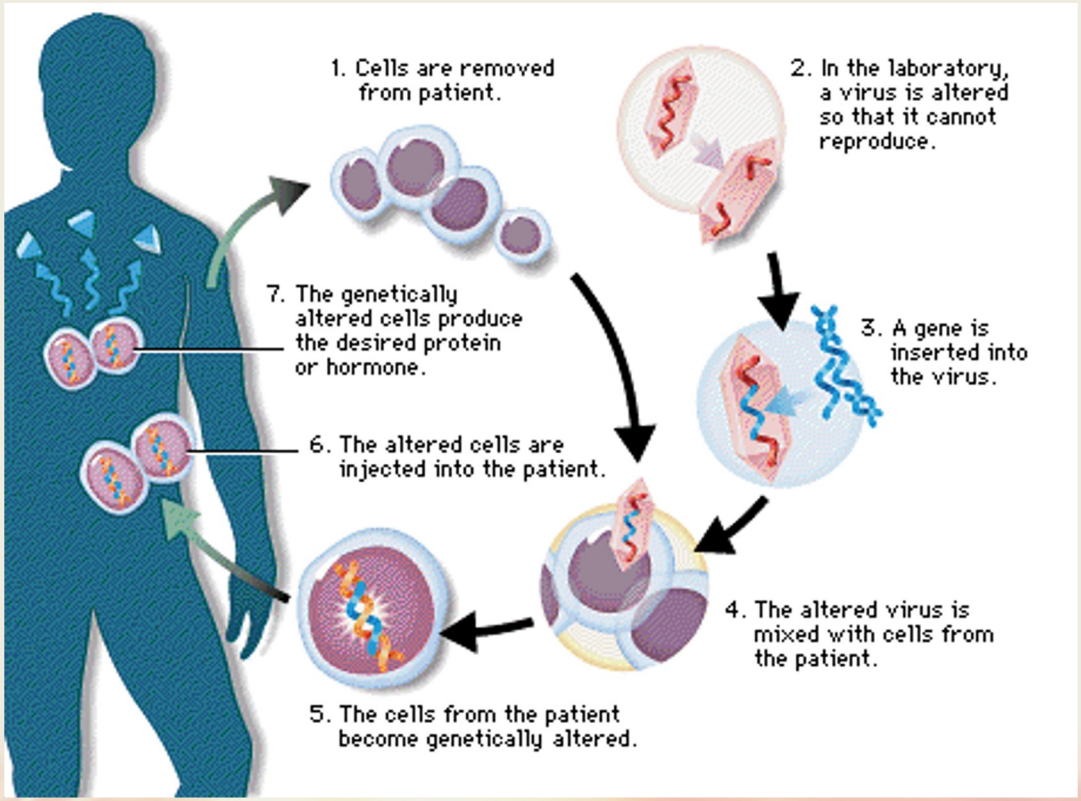
- Historically, a general route to drug design:
  - Identify disease
  - Identify drug target
  - Identify lead compound
  - Create library of possible drugs
  - Test and retest to find potential drug
  - Treat patients with identified compound

A Different Kind of Approach

- Gene differs
  - Identify disease
  - Search for gene that regulates cause of disease
  - Transcribe replacement or modifying genetic material
  - Create vector to delivery DNA or RNA
  - Test drug
  - Treat patient with genes and vector

Gene Therapy

- Most common technique involves insertion of a gene(s) into somatic cells



Germ Cell Route

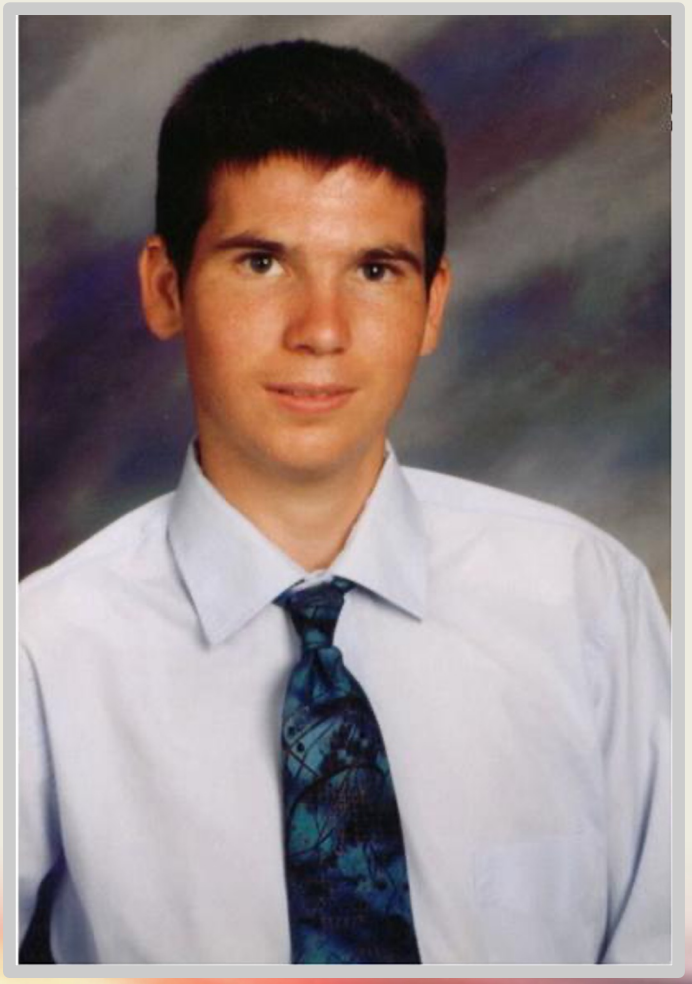
- Modification of sex cells to modify offspring
  - New DNA throughout organism
  - Passed on to all later generations
- Possibility of treating hereditary diseases before conception
- Very controversial

Factors to Consider

- *Safety*: the viral vector needs to have minimal handling risk
- *Low toxicity*: minimal effect on the physiology of the cell it infects
- *Stability*: Minimize amount of genetic variation in virus.
- *Cell type specificity*: modified to target a specific kind of cell.
- *Identification*: Markers, a common marker is antibiotic resistance to a certain antibiotic.
  - Cells not modified cannot grow in presence of antibiotics

Adenoviruses

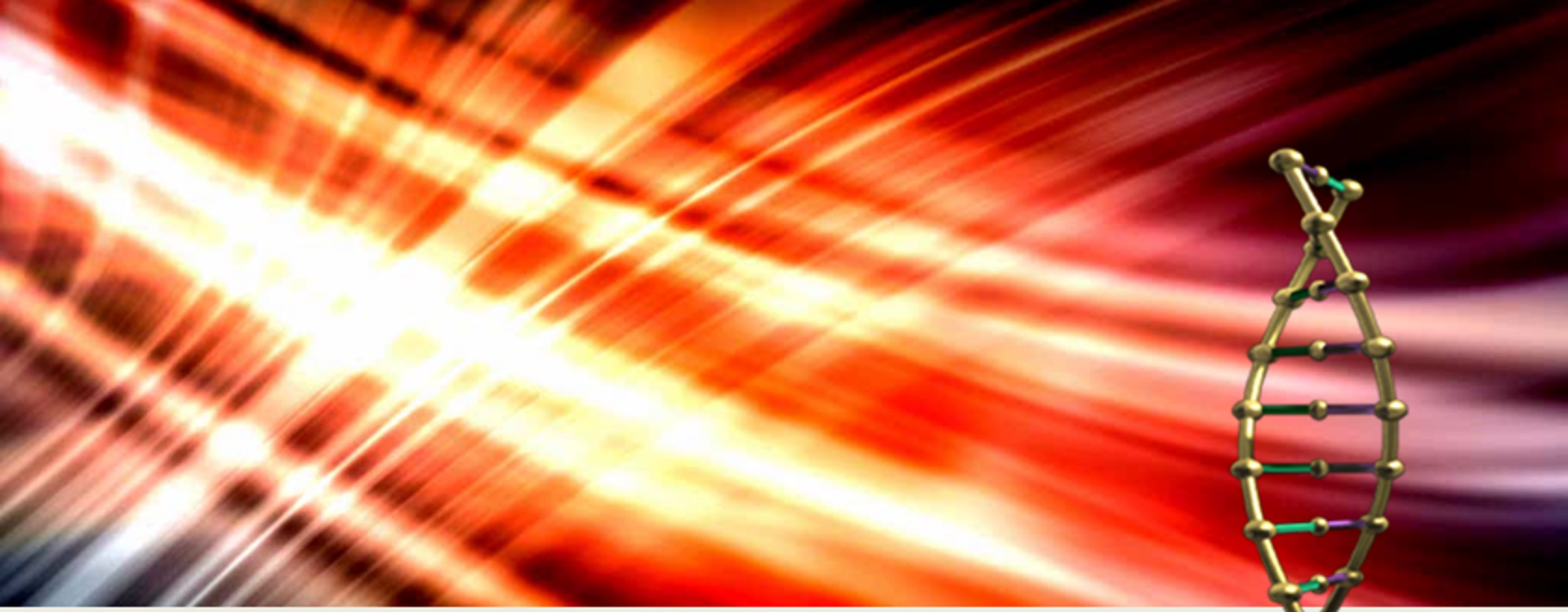
- Jesse Gelsinger
  - Patient in clinical trial
  - Ornithine transcarbamylase deficiency
    - Couldn't metabolize ammonia
  - Administered adenovirus
    - Died 4 days later



Treatable Diseases

- Can only treat diseases that have genetic targets
  - Leber Congenital Amaurosis Hereditary blindness (Spark Therapeutics)
  - Hemophilia https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-adults-severe-hemophilia
  - Spinal Muscular Atrophy

Ex Vivo Gene Therapy



What is Ex Vivo Gene Therapy?

- **Definition**: Altering genes in cells outside the body.
- **Purpose**: Correct genetic defects or enhance cellular functions.
- **Process**: Extract, Modify, Reintroduce.
- **Advantages**: Precision, Safety, Efficiency.
- **Applications**: Blood disorders, genetic conditions.

Stem Cells & Bone Marrow's Role

- **Stem Cells**: Cells with potential to become various cell types.
- **Bone Marrow**: Primary source of body's blood cells.
- **Transplant Purpose**: Replacing faulty or damaged marrow.
- **Chemotherapy Role**: Clear existing marrow, prepare for new cells.
- **Outcome**: Restoration of normal cell production.

The Bubble Boy

David Vetter's Story

- **Condition**: X-linked SCID, severe immune deficiency.
- **Life**: Lived in a sterile environment due to lack of immunity.
- **Attempted Cure**: Transplant from sister.
- **Complications**: Developed Burkitt's lymphoma.
- **Outcome**: Died due to dormant Epstein–Barr virus in transplant.

And when you don’t have a matched sibling?

Four out of five times, there isn’t a sibling match for marrow, and you have to find an alternative donor

New treatment involves transplanting a child’s own gene-corrected stem cells

No graft versus host disease

Bubble boy disease

A boy with Severe Combined Immune Deficiency (SCID) from Argentina

A couple in Argentina had a boy with SCID, who died from a routine immunization.

They had another boy who was healthy, then A.C. was born June 2010 and diagnosed with SCID

No bone marrow matches in family or in ~17 million donors in the worldwide bank

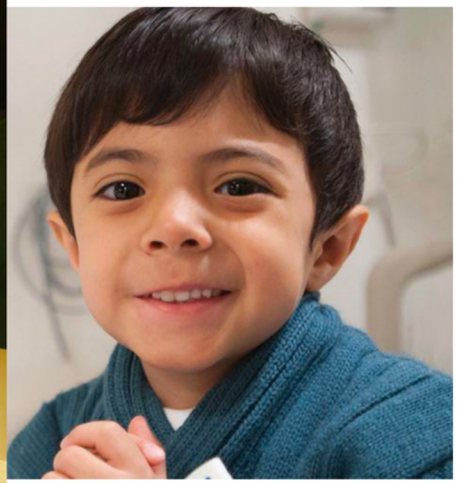
His doctor reached out to Boston Children's for help and he was enrolled on a trial of gene therapy for X-linked SCID (D.A. Williams Sponsor, S.-Y. Pai PI)

A normal life after gene therapy

5 months post

2 years post

5 years post



In school, thriving, no serious infections

Understanding Sickle Cell Disease

- https://www.youtube.com/watch?v=wsykWqyXSKM

- **Nature**: Genetic mutation affecting red blood cells.
- **Symptoms**: Pain, fatigue, organ damage.
- **Complications**: Stroke, infections, vision problems.
- **Life Impact**: Chronic pain, reduced life expectancy.
- **Diagnosis**: Blood tests, family history.

Traditional Treatment: Matched Sibling Transplant

- **Donor Challenges**: Only 20% have a matched sibling.
- **Donor Statistics**: 1 in 4 chance among siblings.
- **Effectiveness**: Potential complete cure.
- **Risks**: Rejection, complications, limited donor pool.

Exploring Alternative Therapies

- **Unrelated Donor Transplants**: From non-siblings but higher graft-versus-host disease (GvHD)
- **Gene editing**: Experimental approaches
- **Gene Therapies**: Modify genes to correct disorders.

Bluebird's Approach

- https://www.bluebirdbio.com/our-science/our-approach-to-gene-therapy

- **Method**: Use of viral vectors to insert genes.
- **Potential**: Lifelong cure without medication reliance.
- **Current Status**: Ongoing trials, promising results.