WHAT IS GENE THERAPY?

Imagine that you accidentally broke one of your neighbor’s windows. What would you do? You could:

1. Stay silent: no one will ever find out that you are guilty, but the window doesn’t get fixed.
2. Try to repair the cracked window with some tape: not the best long-term solution.
3. Put in a new window: not only do you solve the problem, but also you do the honorable thing.

What does this have to do with gene therapy?

You can think of a medical condition or illness as a “broken window.” Many medical conditions result from flaws, or mutations, in one or more of a person’s genes. Mutations cause the protein encoded by that gene to malfunction. When a protein malfunctions, cells that rely on that protein’s function can’t behave normally, causing problems for whole tissues or organs. Medical conditions related to gene mutations are called genetic disorders.

So, if a flawed gene caused our “broken window,” can you “fix” it? What are your options?

1. Stay silent: ignore the genetic disorder and nothing gets fixed.
2. Try to treat the disorder with drugs or other approaches: depending on the disorder, treatment may or may not be a good long-term solution.
3. Put in a normal, functioning copy of the gene: if you can do this, it may solve the problem!

If it is successful, gene therapy provides a way to fix a problem at its source. Adding a corrected copy of the gene may help the affected cells, tissues and organs work properly. Gene therapy differs from traditional drug-based approaches, which may treat the problem, but which do not repair the underlying genetic flaw.

But gene therapy is not a simple solution - it’s not a molecular bandage that will automatically fix a disorder. Although scientists and physicians have made progress in gene therapy research, they have much more work to do before they can realize its full potential. In this module, you’ll explore several approaches to gene therapy, try them out yourself, and figure out why creating successful gene-based therapies is so challenging.
Ashanti de Silva

In September 1990, four-year-old Ashanti de Silva became famous in the scientific and medical communities as the world’s first gene therapy patient.

Ashanti was born with adenosine deaminase deficiency (ADA). People with this genetic disorder do not produce an enzyme necessary for immune system function. As a result, their immune systems do not work properly and even mild illnesses, such as the common cold or flu, can become deadly.

To begin Ashanti’s gene therapy, white blood cells were taken from her body and grown in culture. A retroviral vector carrying the ADA gene was then added. The retrovirus infected the dividing cells in the culture and delivered the ADA gene. These white blood cells were then injected back into Ashanti’s body where they resumed their normal function. This therapy was very effective in animal trials, but no one knew what the effects would be in a human.

Ashanti’s treatment was a success and to this day she has shown no side effects. Her immune system is functioning normally even though only 20-25% of the type of white blood cells used in the gene therapy trial contain the desired gene. In addition, Ashanti has continued taking low doses of the medication commonly prescribed for ADA as a precaution.

The success of this first gene therapy trial bred much optimism that gene therapy would be an effective treatment for many other disorders in the future.
Jesse Gelsinger

A medical study at the University of Pennsylvania took a turn for the worse in September 1999 when Jesse Gelsinger, age 18, died from complications related to a gene therapy he had received as part of an experimental trial. At the time, this was the first known death directly attributable to gene therapy.

Gelsinger was a voluntary participant in the gene therapy trial whose aim was to treat a fatal liver disorder known as ornithine transcarbamylase (OTC). Jesse had a rare, less severe form of the illness that was managed by diet and medication. Despite the required low-protein diet and taking 32 pills each day, Jesse led a normal, active and healthy life. He hoped that his participation in the trial would later help infants and children with the more severe form of the disorder.

The therapy consisted of the OTC gene packaged in an adenovirus vector. The vector was then injected into an artery that leads directly into the liver. Preliminary studies on mice, baboons and monkeys showed success with this approach, with mild (but temporary) side effects. Before this trial no one had injected adenovirus directly into the human bloodstream. Acting on the advice of the University’s bioethics expert, the designers of the study decided to use only stable adult carriers of the disease as opposed to sick infants. The study would find the maximum tolerated dose of the adenovirus vector in humans by placing participants in three groups, with each group receiving higher dosages in small increments. Jesse was in the study’s last group, hence he received the highest dosage. At the time of Jesse’s injection, 17 people had already been treated, one with the higher dosage that Jesse was given. The previous participants had shown mild side effects but were doing well.

Unfortunately, Jesse was not as lucky. Within 24 hours of the injection, Jesse’s liver began to show serious signs of distress and he slipped into a coma. Despite the research and medical teams’ best efforts, Jesse’s condition worsened as one problem cropped up after another. Eventually, Jesse suffered from multiple-organ-system-failure. Four days after the injection, Jesse’s body had swelled beyond recognition and there was no sign of brain activity. Jesse’s father acted on the advice of the medical team and authorized the withdrawal of life support; Jesse died almost instantly.

The researchers involved in the study determined that there was no evidence of human error and that Jesse’s death was the result of an unusual immune response triggered by the adenovirus. Upon investigation, the two governing agencies responsible for overseeing gene therapy trials in the US found that four monkeys in the preliminary studies had a similar reaction to the gene therapy and consequently died. Researchers modified the adenovirus and lowered the dosage in the human trials as a result.

Jesse’s death opened a number of questions about gene therapy and halted all gene therapy trials in the US for a while. The agencies found that deaths in other, different trials had not been reported because they were thought not to be directly attributable to the treatment itself. Furthermore, reports of adverse reactions or deaths that were reported were kept confidential upon the request of those filing the reports. Many in the scientific and medical community believe that sharing information about gene therapy trials might prevent something like this from ever happening again.
Rhys Evans

In 2000, young Rhys Evans received gene therapy to treat his deadly immune system disorder known as X-linked severe combined immunodeficiency disorder (SCID). As a result of this genetic disorder, Rhys did not produce a protein necessary to create the cells of the immune system, leaving his body defenseless.

A retroviral vector was used to deliver the appropriate gene to blood stem cells (from bone marrow) taken from his body. The corrected cells containing the normal gene were then placed back into Rhys’ body where it was hoped they would begin normal immune cell production.

For Rhys, the treatment was a success. Two years after receiving the therapy his immune system is functioning properly and there have been no side effects. Rhys was cured by this gene therapy.

Two French boys who underwent the same gene therapy were not as lucky, however. Though all appeared to go well after the therapy was administered, both boys later developed leukemia. Researchers showed that this happened because the newly transferred gene had inserted itself into a bad place, interrupting the function of a gene that helps to regulate the rate at which cells divide. As a result, the cells began to divide out of control, creating the blood cancer, leukemia.

This unfortunate side effect did not come as a total surprise to doctors and researchers. The possibility of the gene stitching itself into the wrong location and causing cancer was acknowledged before the trials began, and the risk calculated to be low. The benefits of this treatment seemed to outweigh the risk. The parents of the young children who participated in the study were informed of this risk prior to the treatment.

These two cases were enough to halt gene therapy trials using this particular approach in France, England and the United States in 2002. Furthermore, the National Institutes of Health in the United States recommended stopping all therapies involving a retrovirus vector. Of the 14 boys who received gene therapy for SCID, all are still alive and doing well; the two who developed leukemia have responded well to treatment.