The Promise of Gene Therapy

The History of Gene Therapy

More than a decade ago, gene therapy caused a sensation when it successfully treated an American girl named Ashanti DeSilva. She was only four years old and her disease — called severe combined immune deficiency disorder — meant that she would have to stay under sterile conditions for the rest of her life as she had no immune system. The treatment involved a blood transfusion of a genetically altered version of her own white blood cells to treat her faulty immune system. The treatment was a huge success and Ashanti was able to lead a normal healthy life. It seemed then that gene therapy could be a miracle bullet for all diseases, ranging from cystic fibrosis, to cancer and even AIDS and the public loved the idea.

How Gene Therapy Works

In regular gene therapy treatments, a normal functioning gene is inserted into the genome to replace the abnormal, disease-causing gene. In order to do that, a carrier molecule or vector is used to deliver the modified gene to specific target cells. Viruses, fat molecules and electrical pulses are used as the carrier molecules but only viruses have been found to be particularly effective. This is because viruses are simple organisms that lack the biochemical machinery to reproduce themselves. To survive, they must infect a living cell and insert their own genes, which then instruct the cell to make copies of the virus. For gene therapy, researchers take advantage of this ability to infect cells and insert genes which are lacking or non-functional in the patient to remedy their disease. However, in 1999, a gene therapy treatment involving viruses caused an unprecedented fatality and this badly tainted gene therapy’s reputation.

Gene Therapy Under Scrutiny

Four days after administering the viral concoction, the virus used in the gene therapy treatment for American teenager, Jesse Gelsinger’s liver disorder caused massive organ failure. He became the first person to die as a result of gene therapy. The bad press that followed cast a gloom on gene therapy and scientists became dispirited and unwilling to make public findings unless they felt they were very certain. But Dr. Kan Man Hui, director of Cellular and Molecular Research at the National Cancer Centre in Singapore who is working on brain cancer glioma said, “Although more than 3000 patients have undergone therapy so far, Jesse was the only fatality.” He adds that gene therapy has a far better track record than some drug tests, an example of which is Iressa, a lung cancer drug which in 2003 was connected to 173 deaths in Japan. Reflecting deeply, Dr. Hui adds, “But gene therapy
is a very new discipline, so if anything goes wrong, it is put under the microscope.” Adding weight to that argument, scientists say thousands are killed every day whilst undergoing surgery and other conventional treatments so it is prejudiced to judge gene therapy at such an early stage. Resonating similar sentiments, Professor Malcolm Brenner, of the Departments of Molecular and Human Genetics, and Medicine and Pediatrics at Baylor College of Medicine in the United States said, “There is a lot of stupidity. People, including some scientists have no concept of just how long these developmental procedures will take. It would be decades before gene therapy bears fruit.”

**Problems of the Gene Therapy Process**

The gene therapy process is highly intricate and complicated. Many factors need to be considered; problems may lie with the modified gene or the carrier molecule like in the case of Jesse or even in the target cells receiving the altered genetic material. “This is a very delicate system. We have to balance many, many things,” said Dr. Hui. Scientists are still experimenting with ways to evade the body’s natural immune defense system so as ensure delivery of the gene to the targeted cell. “Gene therapy is like a computer program where we’re still trying to iron out the glitches,” said Prof. Brenner. Furthermore, strict regulations and the high costs — at least S$1.7 million (US$1 million) for a 10-person trial have also hindered research efforts. These factors as well as the bad publicity gene therapy has received means that it is unlikely to become commonplace soon.

**Not There Yet but Many Possible Applications**

Possible benefits and applications of gene therapy are plentiful. A feasible application is in battling cancer. In Singapore, researchers are collaborating with surgeons to see if gene therapy can assist in eliminating tumors. By inserting a killer-DNA into the virus so that it kills the target cancerous cells, the tumor can be reduced in size and surgeons can then remove the growth with more ease. This is also potentially useful for zooming in on cells which maybe surgically out of reach. In addition, gene therapy can be used where conventional treatment methods such as chemotherapy and radiotherapy tend to kill even non-diseased cells indiscriminately. A significant advantage in that gene therapy is highly specific and zeros in on specific cancerous cells whereas chemotherapy and radiotherapy tend to kill even non-diseased cells indiscriminately.

The specificity of gene therapy is because attacking cells are able to recognize molecules found on the surface of the tumor cells and this allows them to zoom in directly for a swift kill. Prof. Brenner, who is working on using gene therapy to treat nasopharyngeal cancer, is making cells in the laboratory that can kill certain viruses found in the tumor cells. The attacking cells do this by detecting certain molecules found on the surface of these tumor cells. Concurrently, Dr. Stephan Russell from the Mayo Clinic in the US is working on using the measles virus known to be a potent tumor killer to treat ovarian cancer. The measles virus which many people are vaccinated against during childhood is used here to transport the killer-DNA. In
addition, his research team has also ingeniously engineered genes within the virus to enable them to follow the progress of the treatment.

Apart from treating cancer, Professor Nagy Habib and his group at Imperial College London are also working on using gene therapy to help buffer the harmful side-effects of conventional cancer treatments. Chemotherapy and radiotherapy works by killing quickly proliferating cells like in cancer. However, immuno-competent cells such as white blood cells which form part of the body’s immune system are produced by the bone marrow which also has a high activity. Thus the treatments actually destroy a patient’s immune system whilst trying to fight the cancer. Hence, scientists are working on using gene therapy to stimulate the patient’s immune system to produce more platelets and white blood cells so as to boost their already weak defenses.

Lastly, with competence in gene therapy, researchers can use the knowledge gleaned to further stem-cell research, says Dr. Kevin Scanton of the Keck Graduate Institute in the U.S. By enabling gene therapy to work effectively and understanding the intricate workings of the procedure, researchers can then a better idea how to turn stem cells which are undifferentiated cells into a myriad of other cells to treat other diseases.

A Miracle Bullet?

ed in the development of gene therapy, research is ongoing and scientists are hoping that the positive results will eventually speak for themselves. As Dr. Stephan Russell sums it up, “The field has continued to grow and, for me, it’s not a question of whether gene therapy is going to be successful but how long it’s going to take.” Gene therapy holds much promise but perhaps it is still in its infancy stage and will take years of research and trials to become a safe and mainstream treatment.