

**“Medical Science and Medicinal Science” field**

**Achievement : Proposal of the concept of gene therapy and its clinical applications**

**Dr. Theodore Friedmann**

Born: June 16, 1935 (Age: 79)  
 Professor of Pediatrics, University of California San Diego,  
 School of Medicine

**Prof. Alain Fischer**

Born: September 11, 1949 (Age: 65)  
 Professor at Collège de France,  
 Director of Institute Imagine, Hôpital Necker-Enfants malades

**Summary**

“Injecting genes or gene-transduced cells into a human body for the purpose of treating diseases” is called gene therapy. In the last few years, there has been a series of reports on convincing clinical efficacy of gene therapy in patients suffering from difficult-to-treat diseases, such as congenital diseases and intractable neurological diseases. The origin of gene therapy can be traced back about 40 years ago to 1972, when Dr. Theodore Friedmann published an article on the revolutionary therapeutic concept and research procedure in a scientific journal. In the years following that event, many researchers carried out fundamental research. Clinical studies started in 1990, but no convincing clinical efficacy could be established. After a period of trial and error, in 1999, Prof. Alain Fischer successfully implemented a hematopoietic stem cell gene therapy on patients with X-linked severe combined immunodeficiency disease with dramatic results, proving the efficacy of gene therapy. The vision of gene therapy as portrayed by Dr. Friedmann and the empirical study carried out by Prof. Fischer paved the way for the present gene therapy.

**Delivering a normal, therapeutic gene into a defective cell by using a virus as a carrier**

Humans differ in many properties, such as height, hair color, and some have a tendency to be overweight while others don't. The reason is that the information inscribed in our genes differs slightly from person to person. Sometimes an abnormality in the gene can cause an inherited disease. For example, if the gene producing adenosine deaminase (ADA), an enzyme related to nucleic acid metabolism in the cell, has an abnormality, lymphocytes which control the immune system cannot proliferate even after birth, so that without treatment, the individual would have severe immunodeficiency. Hemophilia and muscular dystrophy are also examples of typical congenital diseases.

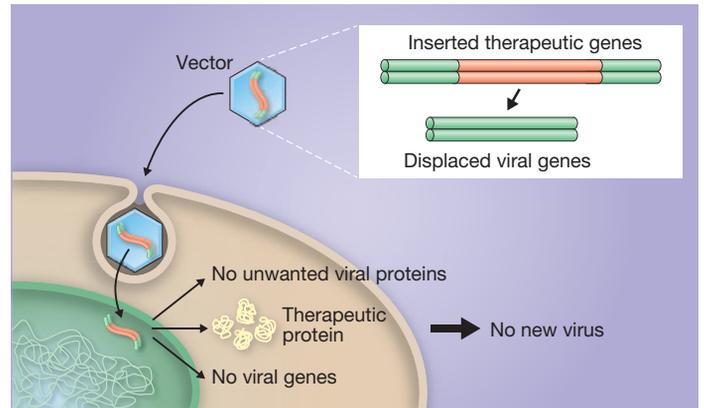
In treating such diseases with few effective treatment options, progress in the field of “genetic engineering” provided a ray of hope. In the early 1970's, the technology of isolating desired genes and transducing them to cells was developed. Many clinicians anticipated that “inserting normal genes to patients would lead to a fundamental cure for congenital diseases.”

Amid such a climate, it was Dr. Theodore Friedmann, an assistant professor at the University of California, San Diego, who set the course for the realization of gene therapy based on scientific data.

For example, what is required in gene therapy is “safely transducing the target gene into the patient's body” and “long-term stable gene expression within the body.” In 1972, Dr. Friedmann and his colleague, Dr. Richard Roblin, co-authored an article in the Science journal. In the article, they explained the concept and importance of gene therapy, as well as the importance of the method using a virus as a gene delivery vector in injecting normal genes into the patient. They also indicated that there were many obstacles to be cleared before it could be put into clinical application.

The word “vector” originates from a Latin word meaning “carrier.” A virus multiplies by transducing its genes into the cell it infects and using the cell's function. The idea is to use this virus as a carrier to deliver the desired therapeutic gene into the defective cell in order to

**Figure 1 : What is an ideal gene delivery vector?**



Ideal treatment as advocated by Dr. Friedmann. Viral genes are replaced with therapeutic genes to convert a virus into a safe therapy vector, which infects the target cell. The transduced genes synthesize therapeutic protein, but no unwanted viral proteins that cause side effects, since vital genes from the virus are removed. Source: Overcoming the Obstacles to Gene Therapy by Theodore Friedmann, Scientific American, June 1997

recover the lost function. Among such viruses, retrovirus has the characteristic to be able to insert a gene into the cell chromosome, enabling a relatively stable gene expression to take place. Thus, retroviruses were thought to be the most promising as a gene delivery vector.

**First dramatic clinical effect demonstrates efficacy of gene therapy**

With the advocacy of gene therapy by Dr. Friedmann and his colleagues, researchers worldwide embarked on the study, and anticipation toward clinical application was heightened. In 1982, the U.S. presidential commission for the study of ethical problems in medicine and biomedical research published a report on the social and ethical issues of genetic engineering with human beings, and in 1986, gene therapy guidelines were announced by the U.S. National Institute of Health (NIH).

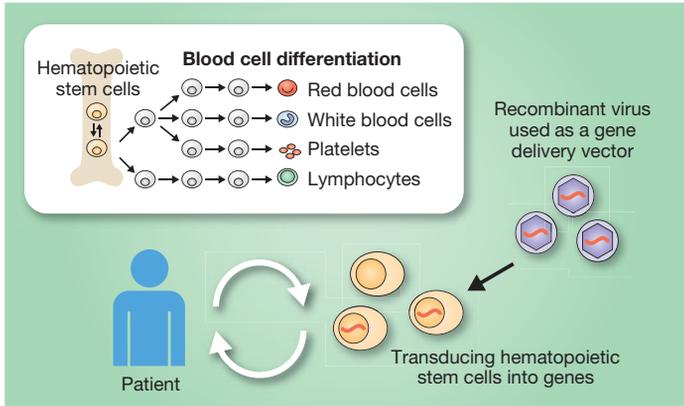
It seemed as if the time was ripe for gene therapy; in the 1990's researchers worldwide were competing to conduct clinical studies. In 1990, the world's first gene therapy was carried out on patients with ADA deficiency, a severe inherited immune system disorder, by a research group headed by the NIH in the United States. In 1995, Hokkaido University in Japan performed gene therapy for the same disease.

However, the initial results of such therapy did not live up to expectations. In 1997, Dr. Friedmann wrote in a scientific journal: “So far no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials. This lack of a convincing therapeutic benefit is sobering.” Reasons cited for the ineffectiveness included that genes introduced into the patients did not reach enough of the appropriate cells and that with time, the transduced genes shut off protein synthesis in the target cell.

While the researchers felt they're at an impasse, a research group headed by Prof. Alain Fischer, Director of the Department of Pediatric Immunology at Hôpital Necker-Enfants malades in France, achieved a breakthrough. He successfully performed gene therapy on patients with X-linked severe combined immunodeficiency disease (X-SCID), an inherent immune system disorder caused by a defect on the X chromosome.

There was a difference in the target cells between the first gene therapy carried out in 1990 in the U. S. and Prof. Fischer's method used in 1999. In the 1990 trial, genes were transduced to lymphocytes extracted from the body and the genes had to be administered many times to maintain a therapeutic level. On the contrary, Prof. Fischer first isolated hematopoietic stem cells of the bone marrow, the source of lymphocytes, and inserted genes into the stem cells. Thus, even with a single administration, the hematopoietic stem cells continue

**Figure 2 : Gene therapy with dramatic effects**



Gene therapy Prof. Fischer performed in 1999 on patients with X-linked severe combined immunodeficiency disease. Normal genes are delivered by a retroviral vector into hematopoietic stem cells, the source of lymphocytes which play a vital role in immunity. This method, through a single administration, enables continuous production of normally functioning lymphocytes, with proven continuous clinical efficacy.

to produce lymphocytes one after another, enabling the patients to recover their immune function in the long run.

The article presented by Prof. Fischer in 2000 provided a strong impact and courage to researchers worldwide. It instilled confidence that when the biological characteristics of the target cells and the transduction vectors were thoroughly examined, there was great potential for gene therapy to play a major part in next-generation medicine.

**Overcoming twists and turns, gene therapy making strides towards practical application**

Even after that time, gene therapy had many twists and turns. Prof. Fischer himself suspended the therapy temporarily in 2002. Four out of 10 patients who were undergoing the therapy were diagnosed with leukemia. In addition, in an altogether different type of gene therapy, there was a fatal incident related to gene therapy in the United States in 1999.

Due to such circumstances, gene therapy had to be carried out with further discretion. Prof. Fischer and his colleagues identified the cause of the problem and implemented safety measures. By means of long-term follow-up on patients, they established the scientific evidence that “regarding severe immunodeficiency, gene therapy has shown efficacy equal to conventional hematopoietic stem cell transplant treatment, and is a safer option of the two.”

After fatal side-effect incidents, clinical studies on gene therapy were stagnant. However, from around 2008, successful cases of gene therapy were successively made public. One new trend of research was the active implementation of gene therapy using an adeno-associated virus (AAV) vector.

In addition, not only were inherited diseases, which were the original target of gene therapy, but it is also noteworthy that the scope of gene therapy was now expanded to include acquired diseases as well. Thus, the idea shifted from “curing the gene” (ultimate gene therapy) to “curing with the gene” (the majority of present gene therapy). In other words, this means not to make abnormal genes normal, but to transduce genes with the desired therapeutic functions. One example of this is gene therapy for Parkinson's Disease. AAV vectors are capable of gene delivery to terminally differentiated cells such as nerve cells which do not divide, thus enabling long-term gene expression. In a clinical study which transduced genes synthesizing a neurotransmitter called dopamine, which is lacking in Parkinson's patients, improvement in symptoms was verified in patients.

Gene therapy is now making significant progress. To get to this point, Dr. Friedmann's foresight with his scientific vision of gene therapy and Prof. Fischer's achievements in realizing that vision both proved to be indispensable.