

Pursuing Gene Therapy for CF

When Cystic Fibrosis Foundation-supported scientists discovered the cystic fibrosis (CF) gene in 1989, they envisioned using normal genes as “drugs” to replace the defective genes to cure the disease. In theory, gene therapy corrects the basic, genetic defect that causes CF, rather than only treating the symptoms. Ultimately, researchers must be able to add **enough** normal genes to CF airways to correct the defective cells with the goal of retaining existing lung function and preventing any further damage.

CF continues to be one of the key genetic diseases studied for gene therapy. Various clinical trials have shown that the normal gene can be safely transferred into CF airways, but scientists are working to develop more efficient delivery methods. While progress in gene therapy continues, scientists also are using their knowledge of the gene and its protein to develop other treatment approaches.

How CF Gene Therapy Works

- Researchers are developing innovative gene delivery systems—or vectors—to determine the best way to deposit healthy genes into the airways of people with CF. These “healthy” genes are manufactured in a laboratory using state-of-the-art biotechnology. Modified viruses that target the airways and compacted DNA are among the vectors being refined for potential gene transfer.
- As an example, the first strategy to evaluate gene therapy in patients used a modified adenovirus (or cold virus) to deposit normal genes directly into damaged CF airway cells. In these experiments, researchers delivered the adenovirus as nose drops, or they drizzled the treatment down a bronchoscope (flexible tube) to reach CF cells lining the airways. Ideally, the healthy gene will be delivered via an inhaled aerosol or through a vein.
- In recent trials, researchers have been testing the safety and efficiency of the modified adeno-associated virus (AAV) delivery system—a method that is less likely to trigger the body’s immune response than the adenovirus. In addition to monitoring safety and efficacy, patients also are monitored to detect whether the normal CF gene has “turned on.” If so, the CF gene should produce a normal protein that can transport ions (charged particles) across the cell membrane, a process that is vital to the health of cells lining the respiratory tract. The AAV trial showed temporary improvement in lung function in AAV-treated patients.
- Another example of a possible gene delivery method is a unique compacted DNA technology, known as PLASmin™, which compresses individual molecules of DNA to their minimum size. These molecules’ small size facilitates uptake of the DNA into the cell and into the nucleus without a virus or other vector to carry it. The unique capability of the PLASmin™ technology appears to be safe when tested in humans and could lead to a successful form of therapy.

Key Advances for CF Gene Therapy

Some of the scientific achievements in CF gene therapy include the following:

- In 1990, one year after the discovery of the CF gene, two teams of researchers corrected CF cells — in lab dishes — by adding normal copies of the gene.

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National Office

6931 Arlington Road Bethesda, Maryland 20814

(301) 951-4422 (800) FIGHT CF Fax: (301) 951-4422 Internet: www.cff.org E-mail: info@cff.org

- In the spring of 1993, the first experimental dose of a gene therapy treatment was given to a person with CF. This study was led by the National Institutes of Health (NIH) and supported by the CF Foundation. It marked the first time that CF scientists were able to test the new laboratory technology in clinics.
- In October 1993, CF Foundation-supported scientists at the University of Iowa achieved another CF gene therapy milestone when they determined that a gene treatment had repaired defective airway cells taken from patients who were treated with the vector.
- In 1995, Targeted Genetics Corporation began a gene therapy clinical trial using the AAV in CF.
- In 2002, after much work and refinement, encouraging results were obtained from a Phase II clinical trial using the AAV. Safety and tolerability of the therapy were demonstrated, along with the first-ever evidence of lung function improvement after gene transfer. Another Phase II trial of this therapy, funded by the CF Foundation and begun in mid-2003, focuses on how well this method works in patients with mild to moderate CF.
- In 2003, a Phase I trial of PLASminTM technology also yielded positive results. Evidence of “take-up” of the corrected gene was seen in the nasal passages where it was delivered. The next step is to aerosolize this therapy to test it in the airways of people with CF.

What’s Ahead

CF scientists are hopeful that some of the same technology being developed for gene therapy to treat airway cells will eventually be adapted to treat other organs affected by CF, such as the pancreas. The first gene therapy experiments involve airway cells because these cells are readily accessible and because lung damage due to CF is the most common life-threatening problem. Any CF gene therapy treatment may need to be repeated periodically to be effective.

Although CF scientists have made remarkable advances, much more research needs to be done to actually cure this complex disease. The CF Foundation has taken the lead in encouraging and funding the necessary research at medical institutions and companies. It also has established the infrastructure through grants and a clinical trials network, known as the Therapeutics Development Network (TDN), to enable the development of new treatments for this disease. The TDN facilitates and expedites clinical trials of all promising CF therapies including the refinement of gene therapy technology. In brief, the CF Foundation continues to support research on a variety of promising treatments simultaneously — gene, protein repair, and drug therapies — to find a cure.

For more information on CF, the CF Foundation, or CF Foundation-funded clinical trials, please visit our Web site at www.cff.org or call (800) FIGHT CF.

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