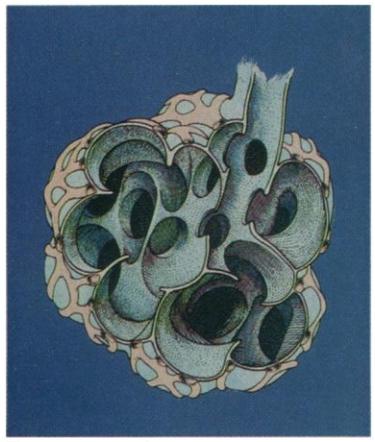
New Vector Delivers Genes to Lung Cells

News about viruses generally comes in two varieties: bad and very bad. But a new approach to gene therapy for hereditary lung diseases shows that viruses have the potential to cure disease as well as cause it.

Researchers at the National Heart, Lung, and Blood Institute (NHLBI), along with collaborators at the Institut Gustave-Roussy and Transgene in France, have used a virus that causes cold-like respiratory infections to deliver a "therapeutic" gene to the lungs of rats. According to Gary Nabel of the Howard Hughes Medical Institute at the University of Michigan Medical Center in Ann Arbor, the work, which is described on page 431 of this issue of *Science*, marks one of the first times anyone has succeeded in introducing a foreign gene into the lung. "This has potential implications for the treatment of many different pulmonary diseases," says Nabel, who is exploring ways to achieve gene therapy for cardiovascular disease. Among the diseases that may be amenable to treatment by the new gene-delivery system are cystic fibrosis and a hereditary form of emphysema, two of the more common—and more lethal—inherited diseases in Caucasians.



Target practice. *Epithelial cells in air sacs are the focus for gene therapy.*

The current work sidesteps some of the potential pitfalls of applying the more commonly used gene-delivery systems to the lung. Most of the research in gene delivery to date has focused on developing modified retroviruses to carry new genes into cells—the strategy used in the first authorized attempts to perform gene therapy on human patients (also see *Science*, 31 August 1990, p. 974). Retroviruses were chosen as gene transfer vectors in these instances for their ability to integrate their own genes—and any foreign genes they might be carrying—into the genomes of the cells they infect. The retroviral gene delivery system may therefore provide a therapeutic gene and the protein it encodes over a long period of time.

Retroviruses might appear to be the vector of choice, and because of its easy access through the trachea, the lung might seem an easy target for gene therapy. But that's not been the case, says Ronald Crystal, leader of the NHLBI team developing the new gene transfer method. The problem is that retroviruses will integrate genes only into dividing cells. And since the majority of lung cells have reached maturity and stopped dividing, says Crystal, they won't acquire a retrovirally transmitted foreign gene.

Another problem is that gene transfer with retroviruses is usually achieved by removing the target cells from the patients, incubating them with the retroviral vector, and then returning them to the patients. But it's not possible, Crystal says, to cull the number of lung cells required for therapy.

Recognizing all these barriers, Crystal's team hit on the strategy of using an adenovirus, which infects lung epithelial cells naturally. Experiments by several researchers had already shown them to be good vectors for introducing new genes into epithelial cells in culture. "There is no question," says Crystal, "that in vitro, in terms of expression, adenovirus is far superior to retroviruses. This is a very powerful vector." But would adenoviruses also transfer genes into living animals?

The new work by Crystal and his colleagues shows that the answer is yes. When they injected an adenovirus containing a gene for human alpha1-antitrypsin into the tracheas of rats, the researchers detected the human protein in the rats' lung epitheliums. Moreover, the cells secreted the inhibitor into the fluid bathing the lung tissue, which for therapeutic purposes is exactly where the team wanted to see it.

The NHLBI workers hope to use their gene-transfer system to treat hereditary emphysema, which is caused by a defective alpha1-antitrypsin gene. Normal alpha1-antitrypsin blocks the protein-digesting action of the enzyme elastase. But as a result of the gene defect, elastase is left uninhibited and eats away at the walls of the lungs' air sacs, causing emphysema. About 2% of the 2 million emphysema patients in the United States have the hereditary disease, Crystal says.

In previous work, Crystal and his colleagues found that weekly intravenous injections of alpha1-antitrypsin improve the conditions of those patients. But, he says, "the intravenous therapy is time-consuming, inconvenient, uncomfortable, and expensive." And that's where he hopes adenoviral-based gene therapy will have the edge. It might produce longer lasting results and it also might be possible to deliver the gene-carrying virus to the lungs in an easily administered aerosol spray.

"The importance of [Crystal's] work is that it establishes the concept that you can deliver genes into lung cells in vivo," says Nabel. "It is an important step forward, but there still is a way to go."

Two questions loom large. Is the virus delivery effective? And is it safe? With regard to effectiveness, Nabel points out that it's "not clear that the virus got into as many cells as would be needed in a therapeutic situation, but it establishes the feasibility of such an approach in vivo." Crystal adds, "We haven't yet tried to optimize the conditions to improve expression. We think we can get much higher levels of expression." It would also help if the adenovirus genome becomes permanently integrated in the host cells. And that, Crystal says, is not yet known.

The safety of the adenoviral vector also needs to be established. "Some forms of adenovirus contain genes that can transform cells," cautions Nabel. Even though those genes would be removed from an adenoviral vector, it might, in the living animal, recombine with a natural virus to produce a more pathogenic strain. "We don't know everything we need to know," Crystal agrees, but adds, "no human lung tumors are known to be associated with adenovirus."

If the safety issues can be resolved, Crystal might have hit on a system that would also be effective in administering gene therapy to patients with cystic fibrosis, caused by a genetic defect that makes the patients extremely susceptible to lung infections. Nabel is encouraged by the success of Crystal's work, as well as by other efforts to develop gene-delivery systems. "It makes a lot of sense," he says, "to pursue what nature has given us to treat disease."

■ MICHELLE HOFFMAN