Genetic therapy: Just a nasal spray away?

A genetic treatment for some inherited respiratory diseases could one day come packaged in the form of a nasal spray.

U.S. researchers, collaborating with two teams in France, have developed genetically engineered cold viruses that can serve as Trojan horses, carrying healthy genes into genetically defective lung cells. They now report using a tailor-made cold virus to insert a normal human gene into the lungs of rats.

Study director Ronald G. Crystal says he hopes eventually to treat patients with cystic fibrosis or other inherited lung problems by spraying the engineered virus into their nasal passages. "I have no doubt . . . that if we administered it to a human it would work," says Crystal, a pulmonary researcher at the National Heart, Lung and Blood Institute in Bethesda, Md.

His group has devised a way to insert copies of normal human genes into a disabled version of a large, cold-causing virus classified as an adenovirus. Adenoviruses target the lining of the lung, where they can cause diseases ranging from the common cold to pneumonia. Some are also used in human vaccines.

In their experiments, the researchers spliced a gene for human alpha 1-antitrypsin — a protein deficient in some emphysema patients — into adenoviruses that were incapable of reproducing to cause disease. They then squirted solutions containing the engineered virus into the lung passages of rats. Although these rats are as susceptible to colds as humans, the viruses inserted the human gene into the rat lung cells without causing disease.

By tagging cells from the rat lungs with radioactive pieces of human genetic material, the team confirmed that the cells took up the human gene. They also detected human alpha 1-antitrypsin in the rats' lung secretions, using antibodies that would bind to human, but not rat, proteins.

In the April 19 SCIENCE, the researchers report that they found evidence of the human alpha 1-antitrypsin gene in the rat lungs for up to one week after administering the solution. Crystal told SCIENCE NEWS that they have continued the experiments and can still find the gene after six weeks. "We haven't seen it go away," he says.

Despite these successful results, Crystal predicts that emphysema caused by alpha 1-antitrypsin deficiency will probably not be the first human disease treated by nasally administered gene therapy, since the disease is already treatable by other means. In 1987, researchers in his laboratory showed that alpha 1-antitrypsin isolated from donated human blood plasma was effective in treating emphysema. A growing number of the roughly 30,000 U.S. patients with alpha 1-antitrypsin deficiency now receive plasma-derived protein, although the therapy costs each patient between $30,000 and $40,000 a year, Crystal says.

He has set his sights instead on cystic fibrosis, one of the most common incurable genetic diseases. Cystic fibrosis causes a buildup of sticky mucus in the lungs and other organs, which leaves patients vulnerable to life-threatening infections. Crystal's group has begun animal experiments with adenoviruses containing normal copies of the defective gene that causes cystic fibrosis. The results "look promising," he told SCIENCE NEWS, but he declined to say how soon he will seek approval to test the therapy on human patients.

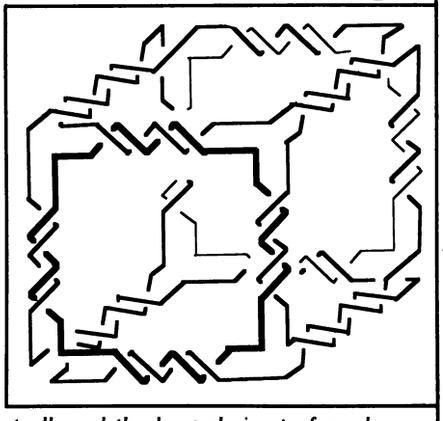
Michael J. Welsh, a cystic fibrosis researcher at the University of Iowa in Iowa City, says the new work "may turn out to be an important step along the way for treating various lung diseases." Welsh led one of the two independent teams that corrected the genetic defect in lab-cultured cells from a cystic fibrosis patient last year (SN: 9/22/90, p.181).

"A very important question will be the safety [of the treatment]," Welsh adds. He cautions that patients could develop allergic reactions to the engineered adenoviruses, especially if the viruses must be administered repeatedly for life.

— C. Ezzell

DNA strands form molecular scaffolding

DNA's twisting strands encode the blueprint of life, but Junghuei Chen and Nadrian C. Seeman are more interested in using them as pieces of a chemical erector set. The New York University biophysicists have constructed a molecular cube by exploiting the ability of unpaired DNA strands to seek out and "stick" to complementary strands. The cube represents a first step toward using DNA to build complex macromolecules tailored for a variety of uses, they assert in the April 18 NATURE.



Seeman/New York University

Chen and Seeman started with two long and eight short pieces of single-stranded DNA, which they had designed on a computer and then synthesized. They first allowed the long chains to form loops. Seeking partners, the loops then linked up with four shorter strands bearing complementary base sequences, creating two squares with double-helix DNA along each edge. The scientists next let the two squares come together. The loose, "sticky" ends jutting out of one square joined with similar ends on the other, forming a flat belt with three adjoining faces. The loose ends at one edge of the belt then folded around to link with the loose ends at the opposite edge, making a cube.

By varying these sequences and increasing the number of strands, Chen and Seeman hope to assemble larger, three-dimensional lattices to use as frameworks for an assortment of custom-designed materials. Such lattices, they suggest, might serve as cages for trapping other molecules, as scaffoldings to hold together loosely connected molecules, or as skeletons onto which other molecules can be attached.

Breakfast may reduce morning heart risk

Skipping breakfast may do more than cut time and calories from the morning routine. A preliminary study suggests people who shun breakfast, compared with those who enjoy a hearty repast, may spend their mornings at higher risk of heart problems, including heart attacks.

Since the mid-1980s, physicians have observed that heart attacks are most likely to occur within a few hours after waking. Although the phenomenon remains unexplained, researchers have proposed several early-morning physiologic changes as potential risk factors. Some point to increases in blood pressure or heart rate, while other studies hint that an increased tendency of blood platelets to clump or stick together when a person gets up in the morning may reduce blood flow in arteries already narrowed by atherosclerotic plaque (SN: 6/27/87, p.409).

Now, cardiologist Renata Cifkova reports data indicating that skipping breakfast may dramatically enhance the early-morning stickiness of platelets.

Cifkova, of Memorial University of Newfoundland in St. John's, says she happened upon this "accidental discovery" while planning a study to measure a protein marker of platelet activity — blood stickiness or susceptibility to clotting — in patients with high blood pres-