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.

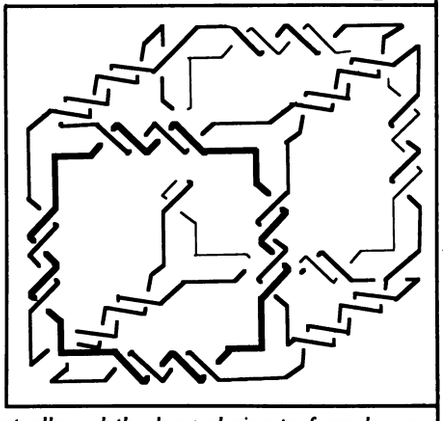
Michael J. Welsh, a cystic fibrosis researcher at the University of Iowa in Iowa City, says the new work "may turn out to be an important step along the way for treating various lung diseases." Welsh led one of the two independent teams that corrected the genetic defect in lab-cultured cells from a cystic 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-

sure. To validate an assay method, she first withdrew and analyzed blood from 20 healthy men and women.

During each of several visits, the healthy volunteers' blood levels of the marker protein, beta-thromboglobulin (beta-TG), averaged about 30 nanograms per milliliter – except in two of the participants. These individuals showed a more than sevenfold increase in beta-TG on one morning. Upon questioning, each recalled only one unusual thing about the day on which their levels were high: no breakfast.

Intrigued by the possibility of a link between fasting and platelet stickiness, Cifkova initiated a small follow-up study, again using healthy volunteers. Between 10 a.m. and noon on two days no more than one week apart, she and her colleagues assayed beta-TG levels in 19 men and 10 women. Participants ate breakfast before coming in for the first test, but skipped it – maintaining at least a 14-hour fast – before the second test. After initial blood tests on that second day, the volunteers ate a meal. Three hours later, the researchers retested them.

Morning beta-TG levels averaged more than 2½ times higher on the day the group skipped breakfast. After they ate, however, the protein plummeted to levels that "did not significantly differ" from those measured after breakfast on the first day, says Cifkova, who presented her findings last week in Washington, D.C., at the National Conference on Cholesterol and High Blood Pressure Control.

While conceding this study is far from conclusive, she says its results strongly suggest that "overnight fasting and skipping breakfast increases platelet activation and might contribute to the known increased frequency of [heart attacks], sudden death and ischemic stroke during early-morning and morning hours."

Noting that other studies have "indirectly suggested that platelets are an important contributing mechanism," cardiologist Syed M. Jafri says he has recently charted the daily cycle of changing platelet stickiness in nine healthy individuals and three people with chronic chest pain, or angina. He and his coworkers at the Henry Ford Hospital's Heart and Vascular Institute in Detroit tracked blood levels of beta-TG and another natural marker of platelet aggregation, called platelet factor 4.

Jafri says the findings, which he plans to present in Amsterdam this June at the International Congress on Thrombosis and Hemostasis, confirm what earlier studies had suggested: Platelet stickiness reaches a daily low overnight, then begins a steep climb when a person rises. Although reduced blood flow can result from activation of either platelets or a separate blood-coagulation system, Jafri's new data indicate that only platelet stickiness varies with the time of day.

– J. Raloff

Huge black hole may lurk in nearby galaxy

Three years ago, a trio of astronomers began observing a celestial object about 300 million light-years from Earth, the likely product of a collision between two galaxies. They had hoped to study the puzzling source of its brilliant, infrared light. Instead, they stumbled onto a far weightier enigma: evidence hinting at the possible presence of the most massive black hole ever postulated to reside within a galaxy. Black holes are dense, compact objects believed to exist but never definitively detected.

Jonathan Bland-Hawthorn of Rice University in Houston and his two coworkers maintain that the simplest explanation for their observations appears to be a black hole as massive as all the visible stars in the Milky Way, yet compressed into a region just one-ten-thousandth our galaxy's volume. But they agree with other researchers that an unusual feature in the relatively nearby galaxy, named NGC 6240, may have more mundane explanations.

Indeed, François Schweizer of the Carnegie Institution of Washington (D.C.) says, "I think there's only a one in 10 chance there's a black hole there."

The astronomers embarked on their odyssey using a special instrument, a Fabry-Perot interferometer. Acting like a highly selective filter, it uses the wavelike properties of light and a variable gap between two polished mirrors to pick out whatever visible-light wavelength the astronomers choose to view. Attached to the 2.2-meter University of Hawaii telescope on Mauna Kea, it enabled Bland-Hawthorn and his colleagues to simultaneously chart the velocity of hydrogen-gas atoms throughout much of the telescope's field of view, allowing the first visible-light map of a predominantly infrared-emitting galaxy.

In the April 10 Astrophysical Journal Letters, the scientists report evidence for two rotating disks of gas in this galaxy. One disk orbits around two light-emitting centers at a speed governed by the mass of the ordinary stars and gas within it. In contrast, measurements from another region some 19,000 light-years away show evidence for a second disk with unusual properties.

The team did not directly view the second disk, but deduced its existence from velocity measurements indicating the presence of a rotating body of gas. From its outer to its inner edge, the gaseous disk increases its rotational speed by more than 400 kilometers per second, the researchers found. They also noted a rise in luminosity toward its center, an indication that more hydrogen gas clusters there.

After a colleague confirmed their results last year, the researchers used elementary physics to deduce the gravitational tug of an extremely massive, dark and compact object – between 40 billion and 200 billion solar masses – hidden in the region enclosed by the disk.

Keel, P.L. Shopbell

Ellipse marks position of central gaseous disk in NGC 6240. Rotational velocity of a second disk (not shown) suggests the presence of a black hole (cross).

Cramming several trillion brown-dwarf stars or neutron stars into the tiny region enclosed by the disk would also explain the findings, Bland-Hawthorn says. But he suspects such a concentration of stellar material would not survive without collapsing into a black hole.

William C. Keel has also extensively studied NGC 6240. An astronomer at the University of Alabama in Tuscaloosa, he notes that the character of this galaxy – believed to be in the final throes of forming from the merger of two others – must be carefully considered in interpreting the current work. The black-hole scenario depends on the assumption that Bland-Hawthorn's team really detected a rotating disk of gas, he explains. "If they're being fooled, if the motion in this merging system [merely looks like a disk], then this is just a case of inappropriate interpretation."

Schweizer says several possible discrepancies point to another explanation. Noting that the researchers admit in their article that parts of the second disk have a relative drop in velocity that can't be explained by simple, planet-like motions, he questions their ability to deduce the presence of a black hole. Instead, Schweizer suggests that material blown out radially from a common center might account for the velocities measured by the researchers. To date, neither Bland-Hawthorn nor co-worker Andrew S. Wilson from the University of Maryland in College Park have ruled out such a possibility.

Bland-Hawthorn told Science News his team hopes to study NGC 6240 with the X-ray satellite ROSAT. Together with higher-resolution observations they made from Mauna Kea last month, these new data might resolve the galactic mystery by the end of the year. *– R. Cowen*