Cystic Fibrosis Treatments Promising

With the unveiling of two promising treatments, some surprising molecular insights, and the apparent success of a gene therapy experiment, researchers last week boosted their already upbeat sense that they are winning the war against cystic fibrosis (CF).

The new reports augment a wave of optimism that began 18 months ago, when scientists found the faulty gene that causes the inherited disease. Striking one in 2,500 U.S. infants, CF causes mucus to accumulate inside the lungs, providing a rich environment for fatal lung infections in the first few decades of life.

Researchers described the new treatments, which seek to prevent lung infections and improve pulmonary function, at a conference in Bethesda, Md., sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the Cystic Fibrosis Foundation. One approach takes aim at a problematic enzyme called neutrophil elastase, secreted in massive amounts by well-intentioned but overstimulated white blood cells in the lungs of CF patients. At high concentrations, the enzyme damages lung tissues and suppresses anti-bacterial immune responses.

NHLBI pulmonary specialists Noel G. McElvaney and Ronald G. Crystal led tests of a neutrophil-elastase-destroying enzyme called alpha-1 antitrypsin in 24 CF patients. Inhaled as an aerosol twice daily for one week, alpha-1 antitrypsin lowered neutrophil elastase levels in the lungs and improved the ability of white blood cells there to kill lung-infecting bacteria. Details of the treatment, which caused no noticeable side effects, appear in the Feb. 16 LANCET.

A second novel treatment targets another CF complication. Large numbers of white blood cells die while ridding the lungs of bacteria. As the cells break down, they dump their DNA into the lungs where it accumulates and clogs bronchial passages. To help clear the lungs, scientists are experimenting with twice daily inhalations of a genetically engineered, DNA-destroying enzyme called human DNase.

In a study of 24 CF patients receiving DNase for six days, the enzyme significantly improved lung function while leaving DNA inside living cells unharmed, says NHLBI's Richard C. Hubbard. Researchers at NHLBI and at the University of Washington in Seattle plan larger trials to determine optimal dosages of the enzyme.

Other advances build on scientists' newfound ability to insert the CF-causing gene, CFTR, into cultured cells, allowing direct studies of its function. Conventional scientific wisdom had held that in normal individuals the CFTR gene makes a protein that controls the opening and closing of molecule-sized tunnels – ones that meter the movement of chloride ions into and out of cells. Scientists thought that the mutated CFTR genes found in CF patients do a poor job of regulating these chloride channels, causing the cellular salt imbalance underlying CF symptoms.

To analyze CFTR's true role in cells, Michael J. Welsh and his colleagues at the University of Iowa College of Medicine in Iowa City inserted the CFTR gene into mouse, hamster and human cells and did cell-membrane studies. A team led by John R. Riordan of the Hospital for Sick Children in Toronto conducted similar tests with insect cells. Both say their results now strongly suggest that the CFTR protein not only regulates chloride channels but is itself a chloride channel.

The odd discovery of a chloride channel that regulates itself leaves scientists somewhat puzzled. Some suggest it could complicate the search for new CF drugs. But Welsh takes a neutral stance toward the finding, arguing that any improved understanding of CFTR's true role can only speed development of effective therapies. His work is detailed in the Feb. 8 SCIENCE and Riordan's appears in the Feb. 22 CELL.

Finally, in a report that hints at the feasibility of a permanent cure for cystic fibrosis, NHLBI's Crystal reported the first successful use of a virus to insert normal, human CFTR genes into the lung cells of living animals. Crystal's team used a partially disabled adenovirus – a type of virus that easily infects lung tissues – to carry the therapeutic gene into cells lining the lungs of three cotton rats. The rats' lung cells produced the normal human protein for at least 10 days. The team has also established they can insert the gene into cultured human bronchial cells.

The work suggests that a deep breath of CFTR-enhanced adenoviruses might someday permanently enable CF lung cells to make normal CFTR. But Crystal warns that scientists still don't know how to regulate the amounts of CFTR made by these cells, and the treatment's safety remains uncertain. *– R. Weiss*

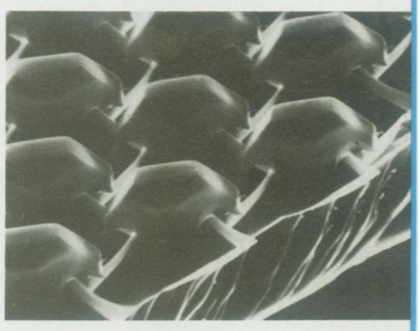
Sticking with silicon micromushrooms

Need to suture a broken blood vessel or securely mount an integrated-circuit chip? The answer to many such sticky problems may lie in new mechanical fasteners consisting of silicon sheets packed with orderly arrays of microscopic structures resembling mushrooms. Just aligning and pressing two such surfaces face-to-face interlocks the mushroom caps to produce a tough, permanent bond.

"It's a very simple idea," says Michael L. Reed of Carnegie Mellon University in Pittsburgh, who is spearheading the fasteners' development. "It isn't hard to make them, and it seems like they just might have a lot of applications."

Reed and his co-workers prepare these novel fasteners by applying the same techniques now widely used for manufacturing dense webs of electronic devices on silicon chips. By selectively etching away portions of a silicon surface initially covered by a thin layer of silicon dioxide, they fabricate an array of silicon dioxide caps perched on silicon pedestals about 5 microns tall.

In one type of fastener, the structures have smooth caps, allowing them to interlock easily. These fasteners provide a way of joining extremely small mechanical objects without using an adhesive. The resulting seals readily survive temperature extremes and chemical attack. Because they practically align themselves, such fasteners may also prove useful in the automated assembly of electronic circuitry.



Reed et al./CMU

Micrograph shows the rounded, mushroom-like structures that interlock when two such sheets are pressed together.

In contrast, structures designed for biological applications have caps with sharp points – which readily pierce tissue – and flared bottoms that prevent retraction. These microscopic barbs, fabricated on opposite sides of a silicon wafer, provide an ideal mechanism for joining tissues without causing extensive cellular damage, the researchers say. *– I. Peterson*