Cystic Fibrosis Corrected in Lab

Two teams of investigators have used gene transfer to correct the cystic fibrosis defect in cells in culture, opening the door, at least a crack, for gene therapy.

"We are talking about years, not decades any longer," says a clearly elated Robert Beall, vice president and medical director of the Cystic Fibrosis Foundation. "We hope this will move CF up the list of diseases that are candidates for gene therapy." Cystic fibrosis is the most common fatal genetic disease in North America.

Announcement of these results follows by just 1 week the first attempt at human gene therapy—an experiment at the National Institutes of Health that Beall believes goes far toward removing some of the social and ethical obstacles to this strategy, if not the scientific ones.

"There are tremendous hurdles to overcome, but this means that at least we ought to run the race. It suggests it might be realistic to think about gene therapy," says Michael Welsh, a Howard Hughes Medical Institute investigator at the University of Iowa, who led one team along with Alan Smith of Genzyme Corporation of Framingham, Massachusetts, and Douglas Jefferson of Tufts University. Their work will be published in the 27 September issue of *Nature*.

The other team was led by Hughes investigators James Wilson and Francis Collins of the University of Michigan and Raymond Frizzel of the University of Alabama, Birmingham. Collins was part of the team that discovered the cystic fibrosis gene last year. The Michigan group's paper was published in the 21 September issue of *Cell*.

Although the two teams took different tacks to insert the normal gene into the defective cells, both achieved essentially the same result: they opened up the chloride channel that is plugged in cystic fibrosis. Because of the closed channel, chloride cannot exit and water is pulled into the cell, leading to the buildup of thick, dry mucus in the lungs that is characteristic of the disease.

The Michigan group used a retrovirus to ferry the gene into a pancreatic cancer cell line derived from a cystic fibrosis patient. The gene was stably inserted into the chromosome and began churning out its protein product, known as cystic fibrosis transmembrane conductance regulator, or CFTR, which then stimulated the channel to open. The Iowa team used a modified vaccina virus to insert the gene into airway epithelial cells.

Stunning as these achievements are, translating them into clinical practice won't be easy. First of all, the investigators have to show that the normal gene can be expressed in vivo. They also need an animal model, which four groups are racing to produce; Beall expects success within a year. Then they must ascertain whether opening the chloride channel actually prevents mucus buildup, as they assume it will.

Perhaps the biggest obstacle is delivery: "how to get the vector into the airways of a living, breathing person—and do it safely," says Collins. Not only must they get the healthy gene to the right cells, but they must get it there in sufficient quantity to correct enough cells for the airway to begin functioning normally. "That is not a trivial problem," says Collins.

The ideal strategy would be to target the progenitor cells that give rise to the airway cells affected in cystic fibrosis. But unfortunately, says Beall, "we don't know the origin of the cells that are affected."

So, as a sort of interim form of gene therapy, the investigators envision an aerosol containing the normal gene in a suitable vector, which a patient would inhale. It might be possible to get enough of the normal gene into airway cells this way, but the therapy would have to be repeated periodically as these transformed cells die off.

Meanwhile, these new studies have provided indisputable proof that the gene discovered a year ago is in fact the cystic fibrosis gene, says Beall. The new work should also speed efforts to figure out exactly what CFTR does. Some people now think CFTR pumps another compound in and out of the cells, and that the second, yet unknown compound regulates chloride ion transport. "I think we don't know and we need to find out," says Welsh.

Upbeat prognosis: *"We're talking about years, not decades," says Robert Beall.*

Both teams have managed to grow great quantities of CFTR for the first time. And Alan Smith of the Iowa team has now produced antibodies to CFTR in rabbits. Because these antibodies bind to CFTR, they can show exactly where the protein functions in the cell. And once investigators figure out what goes wrong with CFTR in cystic fibrosis, they may be able to design pharmacological strategies to combat the disease. Says Walsh: "We may even find a drug that is better than gene therapy."

■ LESLIE ROBERTS

Partner Found for the Myc Protein

Earlier this month, at the Cold Spring Harbor Laboratory's symposium on the "Origins of Human Cancer," Robert Eisenman of the Fred Hutchinson Cancer Research Center in Seattle scrapped his scheduled talk to describe an intriguing new result from his lab: His group has identified a protein that may provide some long-sought answers to how the *myc* oncogene works.

The *myc* gene is one of the best studied of all oncogenes. And for good reason: A great deal of evidence indicates that alterations in the gene can contribute to the development of a wide range of cancers, including common malignancies such as lung cancers, as well as relatively rare ones, such as Burkitt's lymphoma.

Yet, despite the vast amount of work on *myc*—a Medline search by Eisenman turned up 2700 papers on the gene since the 1970s—researchers haven't been able to figure out exactly what the protein encoded by the *myc* gene does normally in the cell or how it malfunctions in cancer cells. "We have accumulated a lot of interesting facts about the *myc* protein," Eisenman says, "but they don't tell us what the heck is going on." The new protein identified by Eisenman's group may change that, for it appears to be a missing link in the *myc* protein's chain of actions.

myc mavens have long suspected that the protein encoded by their favorite oncogene regulates gene expression. The "interesting facts" accumulated over the years include the finding that the *myc* protein is located in the nucleus, the expected location for a gene regulator. Moreover, the protein sequence includes two structural motifs—a "helix-loop-helix" and a "leucine zipper"—found in certain proteins known to regulate gene activity. Generally two or more of these proteins have to act in concert, and the helix-loop-helix and leucine zipper structures serve