Could science use the common cold to cure cystic fibrosis?

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In 1989 scientists identified the gene mutation that causes cystic fibrosis (CF), which led to the hope that CF lung disease could be 'cured' using gene therapy. The premise of gene therapy is that modified viruses or other gene-based systems could be used to deliver a corrected version of a gene into affected tissues. However, the projected cure has been hampered by the natural ability of the lung to limit the introduction of foreign genes into its cells.

Now, University of North Carolina at Chapel Hill School of Medicine scientists have found what may be the most efficient way to deliver a corrected gene to lung cells derived from CF patients, renewing hope that gene therapy for CF lung disease could be a successful future treatment.

While Cystic Fibrosis is a multiple organ disease, it most devastatingly affects the lung. In people with CF the airways are clogged with mucus that is dehydrated and thicker than normal. The inability to clear mucus from the lung increases the susceptibility of CF patients to lung infections, which results in lung damage. Over the last two decades scientists have developed a variety of viral and non-viral vector systems suitable for delivering a corrected CF gene back into lung cells grown in the laboratory. Several of these vectors systems have been tested in human clinical trials. However, the efficiency of gene delivery achieved in the laboratory has not borne out in the clinical studies, suggesting that the cell models used in the laboratory do not represent the status of the cells in patients' lungs. Scientists have since developed laboratory models

of human lung cells derived from CF patients that recapitulate the architecture and function of the cells prese nt in the human lung. Studies using such cell models have revealed that previously used vector systems cannot deliver the corrected CF gene to enough lung cells to be of clinical benefit to CF patients.

In this new study reported today in *PLoS Biology*, UNC scientists took a different approach and used parainfluenza virus, a virus known to infect human lung cells and to cause common colds. The UNC scientists engineered this virus to contain the corrected CF gene and found that it could deliver this gene to 60-70% of lung cells although only 25% of cells needed to be targeted to restore normal function back to the tissue model. "This is the first demonstration in which we've been able to execute delivery in an efficient manner to a tissue that resembles what is present in the lung," said Ray Pickles, Ph.D., associate professor of Microbiology and Immunology at the Cystic Fibrosis Research and Treatment Center and the Department of Microbiology and Immunology. "When you consider that in past gene therapy clinical trials, the targeting efficiency has been somewhere around 0.1 percent of cells at best, you can see this is a giant leap forward.

"We discovered that if you take a virus that has evolved to infect the human airways, and you engineer a normal CF gene into it, you can use this virus to correct hallmark CF features in the model system that we used," he said. For instance, the experiment restored the cells' ability to hydrate and transport mucus secretions making the CF cells function essentially like normal cells.

Now the researchers must work to ensure the safety of the delivery system. In a pleasant surprise, simply adding the CF gene to the virus significantly attenuated it, potentially reducing its ability to cause an inflammatory reaction. But the scientists may need to alter the virus further. "We haven't generated a vector that we can go out and give to

patients right now," Pickles said, "but we are slowly but surely moving forward towards this goal" Pickles says. "It is going to require a long term commitment from the CF gene therapy field that has achieved so much this far and it's only a matter of time until we understand how to do this reproducibly and safely".

Zhang L, Button B, Gabriel SE, Burkett S, Yan Y, et al. (2009) CFTR Delivery to 25% of Surface Epithelial Cells Restores Normal Rates of Mucus Transport to Human Cystic Fibrosis Airway Epithelium. *PLoS Biol* 7(7): e1000155. doi:10.1371/journal.pbio.1000155

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