Forbes.com

Health

Breathing Easier

Mary Ellen Egan 09.18.06

Two new drugs may be the first to halt the progression of a deadly disease.

Tanner Buck is 6 years old. He will be lucky to be alive at age 40. Buck, a wiry little boy with long, lank cornsilk hair, is one of 30,000 young Americans with the fatal genetic disease known as cystic fibrosis. It drowns the lungs in abnormally thick, sticky mucus and devastates the pancreas, liver and other organs.

In between soccer games, tree-climbing and other boyhood pursuits in his hometown of Luck, Wis., Tanner spends part of each day just fighting to breathe. His current treatments are difficult and time-consuming--and aim only at easing the severe symptoms of CF.

Now two publicly held biotechs--Inspire Pharmaceuticals of Durham, N.C. and Vertex Pharmaceuticals in Cambridge, Mass.--are testing new compounds that are the first to target the underlying defects that threaten the life of Tanner Buck. The boy took part in a 90-patient trial of Inspire's new drug in the spring and hopes to reenroll; his mom says the main upside for him is that the experimental regimen lets him watch an extra 45 minutes of TV each day.

Without a new breakthrough, Tanner squeezes life in between daily therapy. To keep his lungs clear, he puts in half an hour twice a day wearing a nebulizer mask and inhaling a mucus thinner (Mucomyst) and a compound that opens up his airways (Albuterol). While inhaling the compounds, he wears a vibrating vest that loosens the mucus in his lungs, letting him expel it by coughing.

In addition to lung therapy Tanner and other people with CF take enzyme pills with meals and snacks to free up the clogged channels that normally carry enzymes to the intestines to digest food; otherwise patients risk malnutrition. The existing regimens have extended the life span of CF patients from 14 years in 1969 to 37 years today.

Now researchers hope new compounds may halt the deadly progression of cystic fibrosis. Inspire's drug, denufosol tetrasodium, emerged in the early 1990s from research by Dr. Richard Boucher at the University of North Carolina at Chapel Hill.

The basic malfunction in CF involves a defect in the epithelial cells (which cover and protect various organs, as well as the skin and the digestive tract), particularly the cells lining the airways of the lungs. These lining cells have channels on their outside surface: One lets sodium ions (small charged molecules) flow into the cell, while another pushes chloride ions out of the cell and into the mucus on the airway surface.

In CF patients the outflow of chloride is hindered, the inflow of sodium unrestrained. This disrupts the delicate balance of salt and water on the surface of the lungs' airways, preventing a normal coating of fluid and mucus inside the lungs, pancreas and other organ passageways.

Patients with CF produce a defective form of a protein called CFTR (cystic fibrosis transmembrane conductance regulator) that screws up the inflow/outflow process. Boucher long suspected that epithelial cells have an alternative chloride transport channel; stimulate the right receptor, and he might jump-start the backup channel.

In 1991, after 15 years of searching, Boucher and his UNC lab coats discovered a nucleotide called uridine triphosphate (UTP) that activates this alternative chloride passageway. UTP turns on P2Y2 receptors--protein molecules on the surfaces of mucosal cells. These receptors prompt the cells to secrete salt (which draws water onto the airway surface) and prompt the hairlike cilia on cell membranes to beat faster to sweep mucus out of the airways and into the trachea, where it is disposed of by swallowing or coughing.

UNC licensed the breakthrough to Inspire in 1995. Inspire raised $9 million to develop a compound that would mimic UTP, tapping venture capitalists at Burr, Egan Deleage & Co. (now Alta Communications), Domain Associates and Medical Science Partners. The firm's scientists spent five years developing a synthetic version of UTP, now called denufosol, which can be inhaled through a nebulizer. Compound in hand, the company went public in August 2000; since then its shares have dropped 73%, in part because of higher R&D costs.

Vertex's compound, VX-770, would go a step further than Inspire's drug. It tries to restore function not only to the lungs but also to other organs affected by CF. VX-770 resulted from a five-year collaboration between Vertex and the Cystic Fibrosis Foundation. Vertex landed $13.3 million from the group to work on the compound and received a total of $40 million in foundation grants (although the organization doesn't own an equity stake in Vertex).

Instead of switching on a backup chloride channel like Inspire's drug, VX-770 works directly on the faulty CFTR channel. It targets parts of the CFTR protein involved in the opening and closing of the CFTR channel, propping open the protein to afford a more normal flow of chloride.
In young patients the pancreas and digestive tract also may benefit from the drug, says Vertex Chief Medical Officer John Alam, because the CFTR function is suspected to play a role there as well.

"I think it's a terrific idea," says UNC's Boucher, although he allows that VX-770 is only in early-stage trials. "There's hope now that you could take a pill and fix CF in the lungs, pancreas and other organs," he says. Patients may benefit from both the Vertex compound and Inspire's denufosol, he adds. "In college kids, who typically have significant amounts of lung damage, denufosol can keep the healthy portions of the lung healthy."

If both approaches win federal approval, Inspire's drug would hit the market several years ahead of Vertex's. In July Inspire began enrolling patients for late-stage trials. Preliminary results could come as early as 2008. When 6-year-old Tanner Buck took part in a 28-day trial of the Inspire remedy last May, his parents watched for signs of improvement but saw none; it may be that Tanner was unknowingly given a placebo in the blinded clinical trial.

"He hasn't asked why he has CF or what it means for him," says his mom, Julie Buck. "And since he's so little, we don't see a point in telling him the details. It isn't fair to tell him he may die from the disease someday when we don't know what's going to happen in the future." She adds, adamantly: "We're hopeful that he will live well into adulthood."

By the Numbers

29 States[1] with mandatory CF screening for newborns.
10 million Number of Americans who are genetic carriers of CF.
30,000 Number of Americans with CF.
14 years Average life span of CF patients in 1969.
37 years Average life span of CF patients today.
[1]Includes the District of Columbia.
Source: Cystic Fibrosis Foundation.