Gene therapy for cystic fibrosis patients

Three teams of scientists received approval last week from a national panel of physicians and ethicists to administer gene therapy to a limited number of adults with cystic fibrosis – the most common lethal hereditary disorder in the United States.

The National Institutes of Health's Recombinant DNA Advisory Committee (RAC) voted to allow each team to squirt solutions of genetically engineered cold viruses into the nasal passages and lungs of patients. The scientists hope the viruses will ferry corrected copies of the defective gene that causes cystic fibrosis into patients' airways, reducing production of the thick, lung-clogging mucus characteristic of the disorder.

Cystic fibrosis is most prevalent among whites, striking one of every 2,000 white children born in the United States. Patients experience recurrent lung infections and difficulty breathing because of mucus accretions in the lungs. In some patients, mucus builds up within the pancreas, intestines, or sperm ducts as well, leading to nutritional deficiencies or male sterility.

There is no effective treatment for cystic fibrosis, although physicians are testing several mucus-dissolving drugs. Most patients rely upon daily physical therapy to dislodge lung mucus and antibiotics to prevent infections from occurring within mucus-clogged organs. Nevertheless, few individuals with the disorder survive past age 30.

For years, the exact cause of cystic fibrosis remained a mystery. Most researchers suspected it had something to do with the body's regulation of salt, because people with the disorder have abnormally salty sweat. Within the past three years, however, researchers have identified the gene that, when damaged, causes cystic fibrosis (SN: 9/2/89, p.149). They have also found that the gene – called the cystic fibrosis transmembrane conductance regulator (CFTR) – normally codes for the production of a tunnel-like protein through which cells excrete salty chloride ions (SN: 3/2/91, p.132). When mutated, the gene produces a protein that fails to do the job, creating instead conditions favorable to mucus deposition.

In the new gene therapy experiments, researchers will attempt to correct this defect by inserting functional CFTR genes into cystic fibrosis patients. The three research teams – led by Ronald G. Crystal of the National Heart, Lung, and Blood Institute in Bethesda, Md., and two Howard Hughes Medical Institute investigators, James M. Wilson at the University of Michigan Medical Center in Ann Arbor and Michael J. Welsh at the University of Iowa College of Medicine in Iowa City – plan to use similar approaches.

First, they will place working CFTR genes inside disabled adenoviruses, which can cause cold symptoms. Because adenoviruses have a specific affinity for the epithelial cells lining air passages in the nose and lungs, the researchers expect them to deliver the genes only to those cells. Disabling the adenoviruses prevents them from multiplying once inside the cells and causing disease.

Each team plans to test the gene therapy in roughly 10 patients over the age of 21 with mild to moderate cystic fibrosis symptoms. Crystal's and Wilson's teams will spray up to four teaspoons of CFTR-containing adenoviruses into the patients' nasal passages and, later, directly into their lungs. Welsh's team plans to squirt the viruses only into patients' noses.

The primary goals of the tests are to determine the safety of administering such gene therapy to cystic fibrosis patients and to find out whether the therapy enables patients' cells to produce functional CFTR proteins. Crystal says the procedure "offers the possibility, albeit low, of clinical efficacy."

However, Crystal cautions that any benefits derived from the therapy will last only a period of months, because the adenoviruses will not insert CFTR genes permanently into the genetic material of the patients' airways. If the initial tests are successful, the teams may ask the RAC for permission to readminister the treatment to the patients later on.

"We're very excited about the prospects of these experiments," says Robert K. Dresing, president of the Cystic Fibrosis Foundation. He adds that cystic fibrosis patients "should be extremely encouraged by the speed with which things are going . . . this could have a real effect on their lives."

All three research teams plan to begin gene-therapy tests as soon as they receive approval from the Food and Drug Administration and NIH Director Bernadine P. Healy. "We could start as soon as early 1993," says Wilson. – *C. Ezzell*

Some hominids show fidelity to the tooth

Among the ancient members of the human evolutionary family, called fossil hominids by anthropologists, *Paranthropus boisei* cuts a striking profile. Its skull revolves around huge jaws that encase small front teeth and immense, peg-shaped back teeth. A flattened face and flared cheekbones slope back to a visor-like crest over the eyes. A bony ridge runs over the top of the head, where it meets a small, triangular braincase.

A new study now indicates that *P. boisei* also exhibited a remarkably stubborn devotion to its distinctive look for more than 1 million years, until the *Paranthropus* lineage hit an evolutionary dead end. The basic features of *P. boisei* jaws and teeth remained unchanged during a time of marked brain growth and tooth-size reduction in direct human ancestors, contends anthropologist Bernard Wood of the University of Liverpool in England.

"I suspect *P. boisei* underwent little evolutionary change of any kind," Wood asserts.

The finding coincides with Wood's view that hominid species directly ancestral to modern humans also experienced few anatomical changes before their relatively abrupt evolution to succeeding species (SN: 6/20/92, p.408).

P. boisei belonged to a group of African hominids, referred to as robust australopithecines by some investigators, which first appeared about 2.6 million years ago. *P. boisei* lived in east Africa from around 2.2 million to 1 million years ago, in Wood's view. Some anthropologists argue that the discovery of the so-called black skull extends the antiquity of *P. boisei* to 2.5 million years ago, a claim that continues to spark controversy (SN: 1/24/87, p.58).

Wood studied 144 fossil jaws and teeth that belonged to *P. boisei* at various points in its evolutionary history. He could not conduct a similar anatomical survey of lower-body bones, because fossil hunters have found a scant collection of such specimens for *P. boisei*.

Only a few, marginally important changes took place over time in the extinct hominid's jaws and teeth, Wood reported last week in San Francisco at the annual meeting of the American Anthropological Association. Nine out of 47 anatomical features measured by Wood displayed significant change in a comparison of early and late *P. boisei* specimens.

Both the thickness and the height of the hominid's powerful lower jaw stayed constant over time, Wood notes. The overall size of the lower jaw increased slightly in later specimens, but the British scientist calls this trend "weak."

In contrast, a few tooth features underwent significant change without altering the crucial aspects of *P. boisei* dentition, Wood asserts. For example, canines enlarged from early to later specimens, but these teeth played a minor role in chewing and grinding, which was handled largely by the heavily enameled molars at the back of the mouth, he maintains.

Although premolar teeth just behind the canines also became larger, no general trends in dental evolution accompany this change, Wood holds.

Anatomical disparities among the teeth and jaws of some *P. boisei* fossils probably reflect differences between the sexes, he says. – *B. Bower*