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## Putting a tumor suppressor back to work

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The gene known as *p53* has been called the guardian of the genome. When a cell turns cancerous, for example, *p53* often turns on and directs the cell to refrain from dividing or, more drastically, commands the cell to commit suicide.

Yet not all cancer cells meekly obey *p53*'s orders. Many silence the gene by deleting or mutating the two copies that most cells possess. Indeed, more than 50 percent of all tumors contain cancer cells having no functional *p53*.

What would happen if scientists popped working copies of *p53* into such tumors? This tantalizing gene therapy strategy has now had its first test in humans, and investigators report that it temporarily prompted tumor regression in three out of seven cancer patients who completed the study, and it checked tumor growth in three others.

These encouraging results were far from a cure, however. All seven men, each afflicted with widespread lung cancer unresponsive to conventional therapies, eventually died of the cancer or complications relating to it.

Still, the primary intent of this initial *p53* gene therapy trial was to establish the strategy's safety, and in that respect, the trial appears a success. "There weren't any toxic effects associated directly with the treatment," says Jack A. Roth of the University of Texas M.D. Anderson Cancer Center in Houston.

Roth and his colleagues packaged *p53* genes into harmless but infectious viruses. They injected those viruses into inoperable, life-threatening lung tumors that had not responded to radiation or chemotherapy.

The hope was that the viruses would infect cells in and around the tumor and deliver a cargo of *p53* genes. Cancer cells, no longer free of *p53*'s influence, would undergo apoptosis, a form of cellular suicide. In contrast, healthy cells receiving an extra copy of *p53* would continue a normal life.

With studies in test tubes and in animals, Roth and other researchers had shown that this strategy bore promise. In the human trial, biopsies of the treated tumor sites showed evidence of increased apoptosis in six of the seven patients, Roth's group reports in the September NATURE MEDICINE.

In several of the patients, the number of cancer cells that died was greater than the estimated number of virus-infected cells. Roth's group had reported a similar result in their earlier studies on animals.

"We see tumor regression that exceeds expectations. That is very surprising," says Roth.

Roth suggests that cells receiving a *p53* gene from a virus may induce apoptosis in neighboring cancer cells. "This is an area of very active research, and we're in

the process of identifying the factors involved," says Roth.

Not all cancer researchers have observed this bystander effect, notes Larry M. Kaiser of the University of Pennsylvania Medical Center in Philadelphia. Kaiser's group has almost completed its own initial clinical trial of the *p53* gene therapy strategy.

In that study, as well as in a new one being conducted by Roth's team, the researchers are using a *p53*-delivery virus different from that used in Roth's initial trial. The new virus, a member of

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## Weight loss pills linked to lung ailment

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Dieters who use certain weight loss drugs may lose more than excess poundage. A study in Europe indicates that fenfluramine and its cousin dexfenfluramine—recently approved for use in the United States—increase the risk of pulmonary hypertension. This ailment damages blood vessels in the lungs, leading to death from heart failure in more than 50 percent of cases.

"The course of disease is rapid deterioration," says Lucien Abenham, a researcher at Sir Mortimer B. Davis-Jewish General Hospital and McGill University in Montreal and an author of the study. Death typically occurs within 2 to 5 years.

The first clue that diet pills might prove deadly surfaced in the 1960s, when a rare lung disease began turning up with unusual frequency in Austria, Germany, and Switzerland. It occurred mainly in women on diets. Doctors soon linked 500 cases of pulmonary hypertension, many of them fatal, to aminorex fumarate, a prescription diet pill.

Three decades later, history seemed to repeat itself in France, although just 15 people became ill and only a few died. This time the culprit appeared to be the appetite-suppressant fenfluramine, which has been used by 50 million people worldwide. This finding prompted Abenham and his colleagues to try to establish a definitive link.

The scientists, from Canada and Europe, compared 95 people who had pulmonary hypertension with 355 people who were not afflicted. They found that people who had taken fenfluramine-derived drugs for more than 3 months had 30 times the risk of the ailment than those who had never taken the drugs.

By taking the drugs for less than 3 months, people doubled their risk of pulmonary hypertension, the team reports in the Aug. 29 NEW ENGLAND JOURNAL OF MEDICINE (NEJM).

Abenham worries about what might happen now that dexfenfluramine has been approved in the United States, where many doctors have come to view

the cold-causing adenovirus family, infects cells more efficiently, says Kaiser.

Another planned modification of the gene therapy strategy is to combine it with radiation or chemotherapy. Some cancer cells that receive a working *p53* gene may not immediately commit suicide, but the added gene may make them more sensitive to conventional treatments, explains Roth.

While *p53*-carrying viruses may aid the treatment of localized tumors, they will likely have difficulty reaching and eliminating cancer cells that have spread beyond the initial tumor site, notes Curtis C. Harris of the National Cancer Institute in Bethesda, Md. —J. Travis

obesity as a chronic disease. In Europe, these drugs are typically used for less than 3 months, says Abenham, who cautions that the European incidents are "nothing like what we might be confronted with in the States, where [the drugs] are prescribed for long-term use."

Though his study does not measure the risks that prolonged users might face, Abenham notes that it suggests "the longer the use, the greater the risk."

The study's ominous results might seem to justify pulling the drugs off the market, but for one fact: Obesity is the second leading cause of death in the United States; only smoking is more deadly. Obesity afflicts 58 million people nationwide, a population that is growing.

Taken together, these concerns raise a thorny question for doctors. Does the risk of taking these drugs outweigh their benefits?

Not at all, say JoAnn E. Manson of Harvard University Medical School in Boston and Gerald A. Faich of the Outcomes Research Corp. of Bala Cynwyd, Pa., in an editorial in NEJM. Taking into account the average weight lost by people using the diet pills, they contend that the drugs save 20 lives annually for each one lost to pulmonary hypertension—or a total of 266 deaths prevented among every million people treated. They also say that the drugs, by decreasing obesity, prevent 400 nonfatal heart attacks and strokes.

Abenham flatly disagrees. "Their calculations are wrong," he says. Saving his specific objections for a rebuttal he plans to address to the journal's editors, he says that Manson and Faich underestimate, by more than half, the risk of pulmonary hypertension in users of fenfluramine-derived drugs.

No one knows why the medicines increase that risk, and the scientific debate over the precise level of risk is unlikely to be resolved soon. In the interim, Abenham and his coworkers say: "We recommend active surveillance of the use of these drugs, especially if long-term use is planned." —S. Sternberg