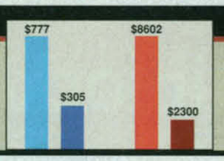


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PLANT BIOTECHNOLOGY

# Seed-Sterilizing 'Terminator Technology' Sows Discord

Plant biotech researchers usually try to give plants a leg up on evolution, packing them with genes to fend off assaults from insects, extreme weather, and herbicides. But the latest innovation to emerge from plant gene labs does just the opposite: It ensures that these attributes won't be passed along to the next generation. Using a neat trick of genetic engineering, companies can now ensure that genetically modified plants produce sterile seeds—a feat that will keep farmers coming back for fresh seed year after year.

Companies say the innovation is needed to safeguard their investments in improved plant varieties, but an array of critics contends that it will further marginalize the world's poorest farmers and erode crop biodiversity. Last week the dispute intensified when a committee for the world's largest agricultural research organization—the Consultative Group on International Agricultural Research (CGIAR)—recommended that its 16 member institutes ban use of the technology in their crop-improvement projects. Although this move is largely symbolic—CGIAR is a nonprofit research outfit that freely gives away its technology—it dramatically raises the profile of the technology's critics. The full CGIAR was expected to adopt the statement this week at its annual meeting in Washington, D.C. And earlier this month, the Rural Advancement Foundation International (RAFI), a vocal farmers' advocacy organization, launched an international campaign against the technology. RAFI is pressing countries around the world to disallow patents on the technique.

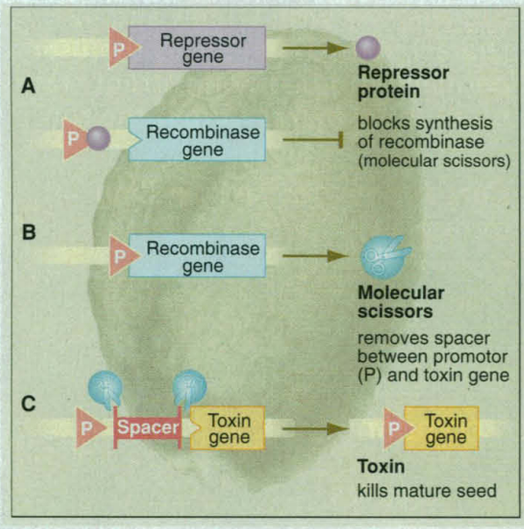
At the heart of this battle is U.S. patent 5,723,765. Issued last March to researchers at a little-known cotton seed company called Delta & Pine Land (D&PL) and the U.S. Department of Agriculture (USDA), the patent covers a technique called the "technology protection system" by its supporters and "terminator technology" by its critics. It involves transferring three genes along with their genetic on switches into the seeds of genetically improved plants. When the master gene of this trio is dormant, the seeds will grow into plants that will produce healthy seeds of their own. But when a company activates the gene before selling the seeds—by exposing them to the antibiotic tetracycline, for example—the seeds produce plants that generate a toxin in their own seeds that kills them (see below).

D&PL's head of technology transfer, Harry Collins, says the technology is designed simply to protect agricultural companies' intellectual property. When farmers save some seeds from a genetically engineered variety for replanting, he says, they are appropriating proprietary technology. Collins says D&PL is currently pursuing the technology for genetically improved varieties of crops such as cotton and wheat and expects it to be on the market around 2005. But in a move that could lead to quicker and more widespread use of the technology, crop life sciences giant Monsanto made a bid in May to acquire D&PL. (The deal is still awaiting approval from regulators and stockholders.)

For seed companies, "it's a delightful profit-making platform," says RAFI head Pat Roy Mooney. But Mooney and others argue that it could be bad news for poor farmers. They point out that subsistence farmers in developing countries, who can't afford industrialized agriculture, often buy small amounts of improved varieties and breed them with local varieties to bolster yields. That practice obviously wouldn't work with sterile plants. CGIAR officials also worry that pollen harboring seed-sterilizing genes could pollinate nearby crops, rendering their seed sterile as well. "That could have a big impact on the world's poorest small farmers" who already live on the margins, says Timothy Reeves, director-general of the International Maize and Wheat Improvement Center, a CGIAR member institute based in Mexico.

But officials at D&PL and the USDA argue that such fears misconstrue the technology. Melvin Oliver, a plant physiologist at the USDA's Agricultural Research Service in Lubbock, Texas, who co-developed the seed-killing technique, says farmers can still store seeds of non–genetically engineered strains and use them to improve local varieties. They just can't do it with genetic improvements that companies have spent millions of dollars to produce. "The system is just to protect new technology," says Oliver. Furthermore, he adds, the technique is currently designed for use with self-pollinating plants that would not spread their pollen and genes to nearby traditional varieties.

Martha Crouch, a seed geneticist and expert on traditional farming at the University of Indiana, Bloomington, says many farmers may have little




**Triple play.** The "terminator technology" causes plants to bear sterile seeds through an interplay between three transplanted genes, one of which produces a toxin that kills seeds in their final stages of development. Researchers first deactivate the toxin-producing gene by splicing a stretch of DNA between the gene and its "on" switch, or promoter. They then transplant this combination into a genetically engineered plant along with a gene that produces a scissorlike protein called recombinase, and a third "repressor" gene whose protein prevents the recombinase gene from being switched on (A). At this stage, the terminator technology is dormant, and the plants produce viable seeds. These seeds are then treated with a stimulant, such as the antibiotic tetracycline, that blocks the repressor protein, and the recombinase gene turns on (B). The recombinase then snips out the DNA spacer between the toxin gene and its promoter, turning on toxin production (C). Plants grown from these seeds will themselves produce sterile seeds.

choice but to adopt the new seeds, however. She points out that large landowners, crop buyers, and government programs often choose the seeds that small farmers have to plant. "Free choice is a nice idea, but it doesn't seem to operate in the real world," she says. She adds that insects commonly spread pollen from self-pollinating crops to other plants, which could put at least a small fraction of a neighboring farmer's plants at risk of being sterilized.

Cary Fowler, a CGIAR delegate from the International Plant Genetic Resources Institute in Rome, Italy, says he is also concerned about the potential threat to crop biodiversity. If the technology reduces interbreeding with local varieties and eventually leads subsistence farmers to switch to genetically engineered crops, some traditional varieties may no longer be planted and will disappear. "You not only restrict the potential improvements, but you may wipe out the farmer's traditional varieties as well," leaving them little to fall back on if disease strikes the engineered varieties, says Fowler. Adds Mooney: "1.4 billion people depend on saved seed for their food security. Companies have to be damned right for them to risk the lives of all those people." Oliver counters, however, that the threat of losing crop biodiversity is inherent in the introduction of any improved crop. The answer, he says, is to increase support for international seed banks to store germ plasm.

At this point, both sides seem to agree on only one thing: that they don't see eye to eye. "Let's face it, there really are two sides to this," says Collins. And both sides seem to be digging in for a long battle.

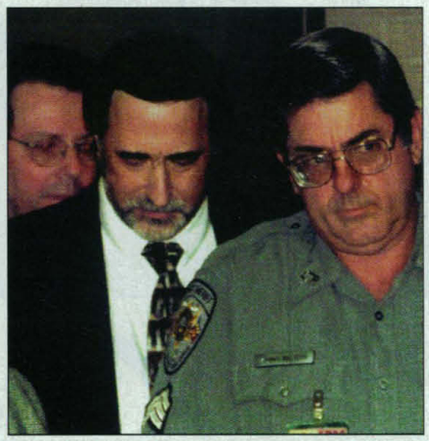
–ROBERT F. SERVICE

FORENSIC SCIENCE

## HIV Strain Analysis Debuts in Murder Trial

A Louisiana doctor was found guilty last week of attempted murder for injecting a former lover with HIV-infected blood. It was an unusual case by any measure, but it was also the first time that a DNA analysis of HIV strains was used in a criminal court in the United States. Although the specifics of this case might be rare, the same kind of evidence could be used whenever the source of a fast-mutating virus is at issue—for example, in cases involving transmission of HIV, food poisoning, or even biological warfare. And expert witnesses on both sides have said that the case points to the need for an explicit set of rules governing the use of such evidence in the courts.

The Louisiana case began in 1995 when Janet Trahan Allen, a nurse in Lafayette, accused Richard J. Schmidt, a local gastroenterologist, of deliberately infecting her with HIV and hepatitis C. She claimed that after she had threatened to break off her decade-long affair with Schmidt, he infected her with tainted blood in place of one of her regular vitamin injections. The blood, the state argued in court, came from two of Schmidt's patients, one of whom had hepatitis C and the other of whom had HIV.



**Convicted.** Richard J. Schmidt leaving court after trial for attempted murder.

As part of its case, the prosecution arranged for an analysis of the HIV strains in blood samples from Schmidt's HIV-positive patient and from Allen. The analysis was performed by Michael Metzker, at the time a graduate student in the lab of molecular biologist Richard Gibbs of Baylor College of Medicine in Houston. Metzker compared the gene sequences of the strains to see how closely related they were, using a technique called phylogenetic analysis. He reported that the strains from the two samples were more closely related to each other than to a set of controls from other HIV-positive patients in the Lafayette area.

Schmidt's lawyers fought to keep the DNA evidence out of the trial (*Science*, 14 March 1997, p. 1559). They argued that the laboratory work had been sloppy, noting that Metzker admitted that two of the control samples had been contaminated with a laboratory strain of HIV. Defense lawyers also said that the analysis was meaningless without a careful epidemiological study of other possible routes of infection. But the Louisiana 3rd Circuit Court of Appeals upheld District Judge Durwood Conque's ruling that the prosecution could use the analysis to support its case.

At the trial last week, molecular biologist David Hillis of the University of Texas, Austin, testified for the prosecution that separate laboratories had redone the analysis on new blood samples and had found similar results. He says he told the jury that although "there's no way in these analyses to absolutely prove a direct transmission from one [person] to another," the "viruses from the two individuals were as closely related as viruses from two people could be." In addition, he said, the strains infecting Allen were a subset of those infecting Schmidt's patient, supporting the case for transmission from the patient to Allen. The prosecution also presented evidence that the seven men with whom Allen had had sex between 1984 and 1995—including Schmidt—had all tested negative for HIV.

Defense witness Bette Korber, head of the national HIV database at Los Alamos National Laboratory in New Mexico, told the jury, however, that the similarity between the strains could have been mere chance. She, with molecular virologists James Mullins and Gerald Learn of the University of Washington, Seattle, had searched a database of HIV strains in Louisiana and had turned up two pairs of infections that appeared to be more closely related than the patient's and Allen's, she said. Those infections, she testified, had no known or probable links to each other.

Korber says she believes the jury understood the limitations of the analysis. "I suspect in this case that the DNA data were interpreted in accord with the way I view it—as inconclusive," she says. Hillis, too, thinks the jurors were persuaded by other evidence, including testimony about a hidden record book that noted withdrawal of blood from the HIV-infected patient and Schmidt's previous threats to Allen and others. "The rest of the case was so strong," he says. "The scientific evidence had little bearing on the outcome of the case."

But both sides say similar cases are bound to arise, and guidelines like those developed by the National Academy of Sciences in 1996 to govern DNA fingerprinting are needed. Korber says such requirements

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