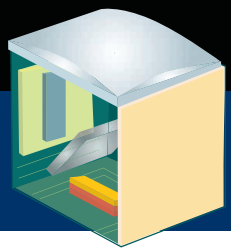
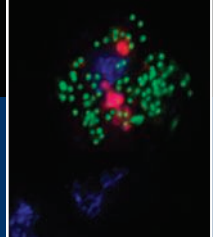


A record-breaking solar cell
583



Amoeba immunity
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CLINICAL RESEARCH

Death Prompts a Review of Gene Therapy Vector

The death last week of a patient receiving experimental gene therapy for arthritis has triggered a federal review of all trials using the same vector. Few details have been made public; if it turns out that the therapy is to blame, it would be another blow to the field's image. Within 8 years, one patient has died as a result of gene therapy and three have acquired leukemia. This would be the first fatality in a trial not studying a life-threatening disease.

The trial's sponsor, Targeted Genetics Corp. in Seattle, Washington, emphasizes that the company doesn't yet know what caused the patient's death. But it would be a surprise if it were the viral vector, says Chief Scientific Officer Barrie Carter, given that the vector has proved safe in hundreds of patients. He and others are watching nervously for the results of an investigation by the company and the U.S. Food and Drug Administration (FDA). Carter believes it could take weeks. "I just hope it doesn't put a mark on the entire field," says molecular orthopedist Christopher Evans of Harvard Medical School in Boston, who is also planning a test of gene therapy to treat arthritis.

The Targeted Genetics trial builds on the success of a drug called Enbrel, a protein-based treatment for rheumatoid arthritis that inhibits a pro-inflammatory cytokine called tumor necrosis factor α (TNF-α). Although Enbrel and similar drugs are effective, they don't always penetrate all joints, and they have to be injected regularly. Targeted Genetics uses a modified virus, called an adeno-associated virus (AAV), to shuttle a gene for the TNF-α inhibitory protein directly into joints. The joint cells then produce the protein, giving patients "a localized depot" of Enbrel that should work long-term, says Carter.

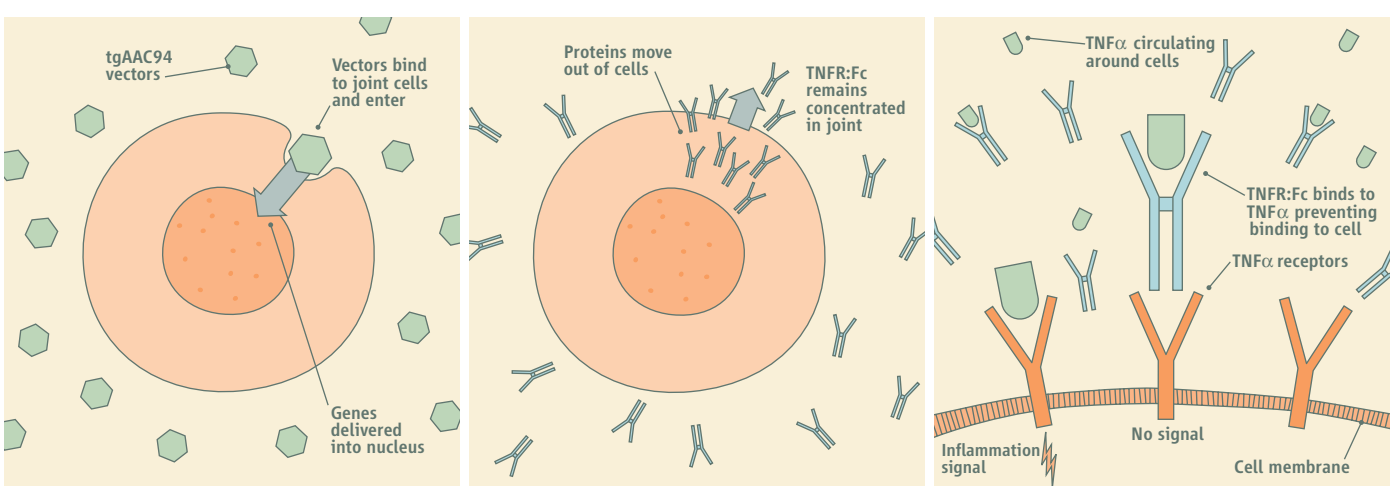
In rats, this strategy "was pretty impressive" at reducing inflammation and inhibiting bone destruction, says Sharon Wahl of the National Institutes of Health (NIH) in Bethesda, Maryland, who co-authored the study with Targeted Genetics. Nonhuman primate data also indicated that the approach was safe. In 2003, NIH's Recombinant DNA Advisory Committee (RAC) approved a safety study in humans. Based on those results, FDA approved a multidose study that began in fall 2005 at about 20 sites around the country.

The trial had enrolled 127 patients (32 on placebo) without any serious side effects, says Carter. Seventy-four had received a second dose. But on 20 July, one patient developed a severe adverse event that "was related in time" to a second injection, FDA says. The agency put the trial on hold; 4 days later, the patient died. FDA is reviewing the 28 other trials using AAV, including 21 active studies.

The tragedy has stirred speculation about the cause. One suspect is the gene product, because Enbrel, which suppresses one immune response, has been linked to sepsis and bacterial infections, suggests gene therapy expert Terry Flotte, dean of the University of Massachusetts Medical School in Worcester. But Carter says the protein is "not necessarily the issue" because the protein has not been detected in serum from nonhuman primates or patients.

It seems equally unlikely that the problem could be the AAV vector, says Carter. He notes that more than 500 patients have safely received AAV since 1992. However, one difference is that patients in the arthritis trial, unlike the earlier ones, received more than one dose. That raises the possibility that the patient became sensitized to the vector, leading to an adverse reaction, suggests Evans. It happened once before, in 2004, when AAV caused a mild immune reaction in two patients who received the drug in the liver (*Science*, 4 June 2004, p. 1423).

Gene therapy has restored the health of about 20 children with severe combined immunodeficiency disease. The approach is showing promise against cancer, too, experts note. "The field is extremely robust," says Arthur Nienhuis of St. Jude Children's Research Hospital in Memphis, Tennessee, and president of the American Society of Gene Therapy. Meanwhile, Carter says his company is "working furiously" to figure out what caused the death before RAC meets to consider the case in mid-September. **–JOCELYN KAISER**



Joint effort. A Targeted Genetics vector (tgAAC94) is injected into arthritic joints; cells then make a protein (TNFR:Fc) that blocks the cytokine TNF-α.

CREDITS: TARGETED GENETICS; (DESIGN) WOODARD AND CO.