

Therapy on trial

The death of a participant in a gene therapy trial has thrown the entire field into question—as it did once before in 1999. Can the field survive this second setback? Virginia Hughes investigates.

Three weeks after receiving a second knee injection of an experimental gene therapy to treat her rheumatoid arthritis, 36-year-old Jolee Mohr lay unconscious at the University of Chicago Medical Center, breathing through a ventilator while her liver gave out. On 24 July, her family opted to remove life support.

Mohr had been transferred to the intensive care unit in Chicago from her local hospital five days earlier, in the middle of the night. More serious than her liver damage was an overwhelming infection that was causing internal bleeding, respiratory failure and kidney failure, says Kyle Hogarth, Mohr's doctor in Chicago.

As Mohr's condition worsened, Hogarth's team tried to locate the infection's source. "[The gene therapy] was definitely on our list of possible causes, because of the timing of her symptoms," Hogarth says. Mohr had already been vomiting and feverish the night after she received the first injection.

Shortly after she was admitted, Hogarth called the US Food and Drug Administration (FDA), which oversees clinical trials in the US, to alert them of her deteriorating status. The FDA immediately suspended the trial, banning further treatments or recruitment of new patients. None of the trial's other 126 participants have experienced serious side effects.

Gene therapy aims to cure diseases by using genetically engineered viruses to deliver functional genes that can replace the faulty ones that cause disease. Scientists have long touted gene therapy's promise, but the approach has shown little success so far.

In 1999, the field took a major hit when 18-year-old Jesse Gelsinger died in a gene therapy trial at the University of Pennsylvania. Mohr's death has once again thrown the field's entire future into question, with bioethicists and scientists questioning whether the risks of gene therapy far exceed its long-promised, but largely unproven, therapeutic benefits.

Mohr's death hasn't yet been definitively linked to gene therapy. A postmortem investigation found *Histoplasma*

capsulatum, a common respiratory fungus, and herpes simplex virus disseminated throughout her body. Neither microbe is normally deadly, but Mohr's immune system may have been weakened by the gene therapy.

On 17 September, the Recombinant DNA Advisory Committee (RAC), a panel of scientists and bioethicists that reviews research protocols and makes recommendations to the FDA, plans to discuss the Mohr case. If her death is proven to be a result of the gene therapy, says viral immunologist Hildegund Ertl, who is a member of the RAC but does not speak on its behalf, "I think it would harm the field—badly."

Tainted past

Gene therapy has had limited success so far. It has repaired the immune systems of an estimated 30 children with severe combined immune deficiency (SCID). This summer, scientists also reported promising safety data from the first trial of gene therapy for Parkinson's disease (*Lancet* **369**, 2097–2105; 2007). And 32 phase 3 trials are underway for various diseases including melanoma, head and neck cancer, and myocardial ischemia.

Since 1990, scientists have led more than 1,300 gene therapy trials worldwide. Only one, in China, has so far yielded a marketable product.

"Investors want quick returns, and it's taken longer than predicted for it to be proven to have therapeutic benefit," says Mark Kay, a Stanford University geneticist who has led two gene therapy trials. But in the long term, "gene therapy's going to be a very important addition in our medical arsenal," Kay says. "There's no doubt in my mind."

Gene therapy was first tested in people in 1990, when four-year-old Ashanthi DeSilva was treated for SCID, or the so-called 'bubble boy disease'. DeSilva is still alive. But scientists say that may be because of a new drug that she also received at the time.

Soon afterward, the number of gene therapy trials—targeted against dozens of illnesses, including cancer—skyrocketed. "Twenty years ago, the field was incredibly upbeat," Ertl recalls. "They thought they could fix it all."

But Gelsinger's death demoralized the entire field. About a third of the members of the American Society for Gene Therapy, the

field's primary professional organization, did not renew their memberships in 2000. Several academic institutions and companies abandoned ongoing gene therapy trials. The FDA initiated an inspectional blitz of about 70 trials—although it later allowed most of them to resume.

Another blow came in 2003, when French scientists announced that gene therapy had repaired the immune systems of ten children with SCID, but had triggered leukemia in two of those children. One has since died, and two others from the same trial have been diagnosed with leukemia.

"Gene therapy has been fraught with disaster," says University of Pennsylvania bioethicist Arthur Caplan. "It's not for want of oversight that there are problems," he says. "The research is just risky."

But some experts say gene therapy is unfairly maligned and is no riskier than other new therapies.

"If the [SCID] story had been a fatal cancer in a handful of patients treated with a new drug," Kay argues, "a cure rate of 60% or 80% would have read differently in the headlines."

Virulent vector

In Mohr's case, the gene therapy was not for a lethal cancer, but for rheumatoid arthritis. An adeno-associated virus (AAV) was twice injected into her arthritic knee, which was swollen because of a buildup of a protein called tumor necrosis factor-alpha. The virus delivered a gene that encodes for another protein that would bind to the factor and reduce inflammation.

About 600 people have so far participated in clinical trials that use AAV vectors. Mohr's is the first to report a serious adverse event.

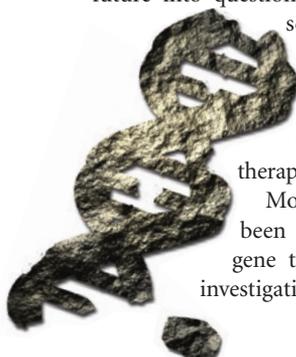
Even if Mohr's death is linked to gene therapy, experts say the AAV vector is unlikely to be the culprit.

Gelsinger's death was proven to be the result of the adenovirus used in that trial. But "there was lots of evidence that adenoviruses could have severe toxic responses in animals," says Kay. "The debate was over the dose."

AAV vectors, in contrast, had never been observed to elicit an immune response in people—until recently.

Researchers have been studying the use of AAV vectors to treat hemophilia, an inherited bleeding disorder. The animal studies looked promising, but when the researchers began testing the approach in people, one woman developed an immune response to the vector's protein shell (*Nat. Med.* **13**, 419–422; 2007).

"It's not terribly surprising that when you go into the clinic, sometimes you uncover things that were not anticipated by the animal studies," says Katherine High, a hematologist at



the Philadelphia Children's Center, who led the study.

In 2001, another team found that a high proportion of mice treated with the AAV vector as newborns later developed liver tumors, prompting the FDA to halt two clinical trials that used the vector. An expert panel later concluded that the tumors were not caused by AAV, and the trials resumed. But when the same team injected AAV into healthy mice, more than half of the mice developed liver tumors, compared with eight percent of untreated animals (*Science* 317, 5447–5477; 2007).

Preliminary findings from Mohr's autopsy investigation suggest that AAV might have contributed to her weakened immune system.

The gene therapy was targeted to Mohr's knee and was supposed to stay confined there because the AAV vector lacks the genes it needs to replicate. "The reason everyone likes using AAV is that it can't grow," says Hogarth. "But it's conceivable, though not proven, that the virus she was injected with was able to replicate because herpes was present."

If AAV did somehow spread—perhaps by hijacking the replicating capabilities of the herpes virus—then the immune suppression triggered by the gene therapy could have activated the fungus, Hogarth says.

However, Mohr was also taking the anti-inflammatory drug Humira (adalimumab), which is known to make people susceptible to the fungal infection.

Hogarth's team is looking for remnants of AAV in Mohr's tissues, as well as for the protein the gene therapy was supposed to make. The final cause of death is not expected to be known until late September.

Ethical questions

When Seattle-based Targeted Genetics first proposed the arthritis trial, the FDA sent a copy to the RAC, as it does for all gene therapy proposals. At a public meeting in September 2003, eight RAC members voted for a closer review of the study. Some members also raised concerns about the AAV vector possibly spreading throughout the body, according to meeting minutes published on the RAC's website.

Committee members also questioned whether such a risky treatment is justified for people with arthritis, a non-life threatening disease, and whether the informed consent documents fully described the risks involved. Finally, they requested a "clearer description of the role of the sponsor and possible conflicts of interest on the part of the investigators."

Responding to these concerns, the company agreed to consider involving a neutral third party in the recruitment and enrollment.

The study was then unanimously approved—

under the condition that when a recruiter was also the participant's personal physician, "an independent third party should discuss the details of the study with the patient and carry out the consent and enrollment processes."

When trial researchers recruit their own patients, "it confuses the line between research and therapy," says Caplan. "Subjects tend to think that what's being offered in the name of safety research is actually

therapeutic." Targeted Genetics officials did not return phone calls made for this article.

Just how much Mohr knew about the risks involved in gene therapy is unclear. But she signed up for the safety trial during an afternoon office visit with Robert Trapp, her rheumatologist of seven years. She signed the 13-page consent form during the same visit, without the counsel of an independent third party, according to her husband.

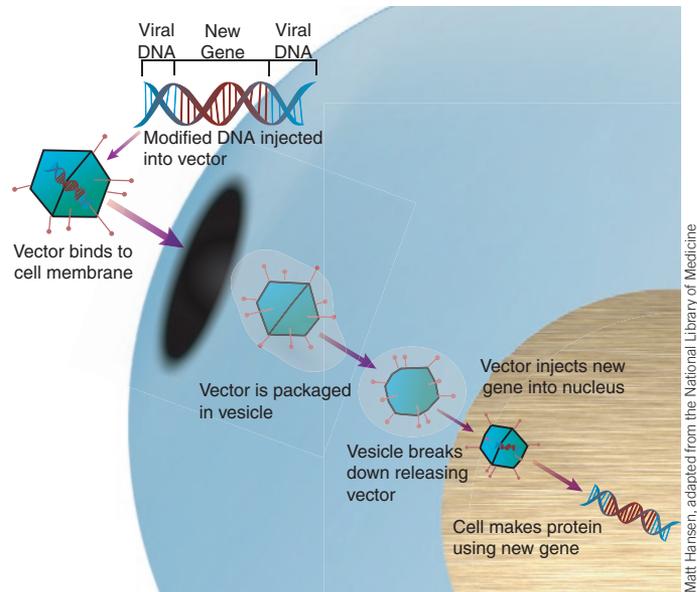
Since her death, Trapp has told her husband that he thought the trial was designed to test both safety and efficacy—it was an early trial designed to assess only safety—and that he had been told so at a training session organized by the company. Targeted Genetics paid Trapp's clinic for each participant recruited into the trial, but Mohr says his wife had not known of Trapp's financial tie to the study. Trapp declined to comment on the case.

"My wife's always been a very quiet, trusting person," her husband says. "But I wasn't there, and can't speculate on what was said between the two of them behind closed doors."

Undue risk

Mohr was taking three standard drugs for joint pain, but her husband says her arthritis was hardly debilitating. She never had trouble playing with their five-year-old daughter, and at her data-entry job, where wages are based on typing speed, she was at the top of the pay scale.

"A lot more thought needs to go into what diseases really are the best candidates for this emerging technology," says Jeff Chamberlain, a molecular geneticist and member of the FDA's



Unproven idea: Gene therapy aims to replace the faulty genes that cause disease with healthy genes delivered by a virus.

Cellular, Tissue and Gene Therapies Advisory Committee.

But others say that rather than passing generalized restrictions, it would be more worthwhile to evaluate each proposal more carefully.

"I'm not sure any change in guidelines or enforcement would have prevented this death," says Caplan. "There's definitely room for more oversight," he says, "but you're never going to eliminate the risk."

In the aftermath of Mohr's death, experts are calling for changes in the way all clinical trials are handled.

For instance, the California-based Center for Genetics and Society, a public interest group, is calling on the FDA to make public all of the information from the Targeted Genetics trial, including full details about informed consent documents and payments to doctors.

Ethical issues aside, High points out that several now-routine technologies, such as monoclonal antibodies and bone marrow transplantation, took a long time to develop. "Sometimes it's not clearly appreciated that it could take as many as 30 years of clinical investigation for something to really become an accepted therapeutic," High says.

Mohr, who does not plan to pursue legal action but will attend the RAC meeting, says he does not blame gene therapy for his wife's death—at least not until there is scientific proof of a direct link. "There's a lot of hope in [gene therapy] research," he says "and the opportunity to help many people."

Virginia Hughes is a freelance writer based in New York.