

Questions linger about unexplained gene-therapy trial death

Gene therapists are waiting nervously for the outcome of investigations into the death of a participant in a pioneering gene therapy trial in Germany, expected in the next few weeks.

One of three individuals enrolled in the trial, set to treat the rare but life-threatening immunodeficiency disease chronic granulomatous disease (CGD), died on 10 April after his colon perforated and consequent septic shock caused organ failure.

Scientists reported the death at the annual meeting of the German Society of Internal Medicine on 26 April, adding that an investigation into the exact cause of death is ongoing.

“The worst-case scenario would be that we never resolve what actually caused the death,” says Harry Malech, a gene

therapist at the US National Institutes of Health. “Then we will all be left with uncertainty.”

CGD, whose victims suffer incessant infections, is caused by a defective *gp91^{Phox}* gene, which prevents normal maturation of leukocytes, a type of immune cell. The therapy a retroviral

involved using vector to insert a replacement gene into blood stem cells.

The cells of the trial participant who died had successfully incorporated the gene and, at least in the first 16 months after therapy, the gene appeared to be functioning. Cells with the gene were able to kill infections *in vitro* (*Nat. Med.* 12, 401–409; 2006).

That individual underwent gene therapy in January 2004 and enjoyed a life without hospitalization until late 2005. The others—one treated in Frankfurt in May 2004 and the other in Zurich in May 2005—are also progressing without severe infections.

The trial investigators have already ruled out

any leukemia-like diseases such as those seen in 2003 and 2004 in gene therapy trials for the so-called ‘bubble boy disease.’

“The death was definitely not a direct consequence of the transferred gene,” says Manuel Grez, the molecular virologist who led the CGD trial. But an indirect effect cannot be ruled out until the investigation is finished.

The researchers are trying to determine the number of gene-modified immune cells to see if they have fallen below levels required to fight infections. And they are testing to see whether the transferred gene has stopped functioning efficiently.

They are also trying to identify the kind of infections in the trial participants. Some infections, such as with the bacterium *Borkhaldia cepacia*, are unique to CDG, notes Malech, and its presence would be an indication that the death was a result of underlying disease that the therapy had failed to cure.

Regulatory bodies have not halted gene therapy trials as a result of the death, but recruitment into the Frankfurt trial is temporarily suspended. Malech has also put on hold his plans to apply for permission to conduct similar trials at the US National Institutes of Health.

Alison Abbott, Munich

Scientists assail South Africa’s ‘vanity’ publications

South African scientists are demanding urgent reform of the country’s research publishing system, following a report that most of its journals have no international credibility.

The devastating analysis, released in May by the Academy of Science of South Africa, found that one-third of the 255 government-accredited journals are essentially vanity publishers, with not a single article in the past 14 years mentioned outside—or even inside—the country.

A six-member panel of the academy in 2004 launched the investigation at the request of the government’s Department of Science and Technology.

South Africa is considered the leading research publisher in Africa, but the Pretoria-based academy found that nine of ten journals are virtually invisible internationally. Fewer than 25 are mentioned in the Institute for Scientific Information (ISI) databases that rank journals.

The report singled out institutions such as the University of Potchefstroom, which until a decade ago was an Afrikaans-language,

whites-only campus under South Africa’s apartheid policy of racial segregation, for particular criticism. “Many journals are written, edited and peer-reviewed by colleagues from within the same university and sometimes from within the same department,” says study co-author Johann Mouton, director of the Centre for Research on Science and Technology at the University of Stellenbosch.

Frans du Preez, a spokesperson for the University of Potchefstroom, which has since merged with a predominantly black university to form the North-West University, concedes that the complaint has merit. It was difficult for researchers working “in the isolation years,” du Preez says, when academic sanctions in opposition to apartheid banned them from international conferences and collaborations.

“Alternative ways had to be created because South African academics were not recognized,” he says. “Perhaps that was the reason why we went that way to create our own publications.”

But neither perceptions of an outsider status nor difficulties with the English language are an excuse for inferior quality, says Dan Ncayiyana, the Durban-based editor of the *South African Medical Journal*, one of the few listed in the ISI.

Not everything in the report is negative. Co-author Anastassios Pouris of the University of Pretoria cites immunology and microbiology, including HIV/AIDS research, as areas in which South African scientists are increasingly producing world-class research.

The academy has asked the department of education to cede some of its control over funding research publications, revamp the system and promote international collaborations.

The report also encourages journal editors to push for open-access online publication in addition to print versions so that scientists worldwide can assess whether their African colleagues’ research is—to use a common South African word for excellent—‘lekker.’

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