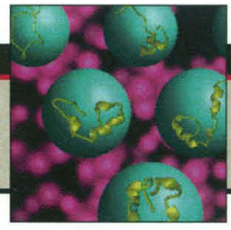
PAGE 2247
Europe's new x-ray vision



2250
IBM's petaflops challenge

CLINICAL TRIALS

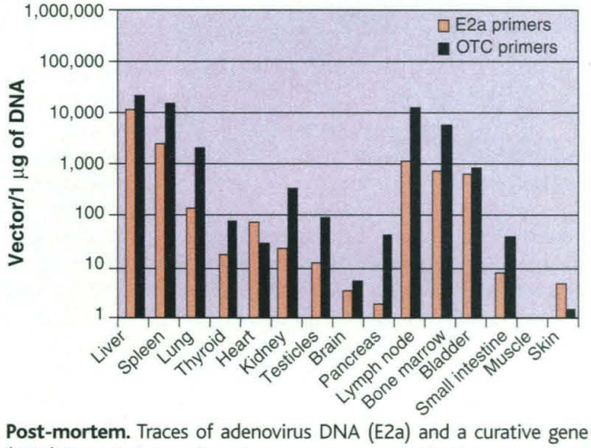
Gene Therapy Death Prompts Review of Adenovirus Vector

For the past 3 months, one-third of the 250 faculty and staff members connected with the University of Pennsylvania's Institute for Human Gene Therapy have been studying a single case. They've been trying to understand why Jesse Gelsinger, a relatively fit 18-year-old with an inherited enzyme deficiency, died on 17 September, 4 days after doctors at Penn injected a genetically altered virus into his liver.

Gelsinger was the first patient in a gene therapy trial to die of the therapy itself, as James Wilson, who heads the Penn institute, confirmed at a public meeting last week. His death is the latest blow to a field that has been struggling to live up to the promise and hype surrounding the first gene therapy trials a decade ago. And Penn isn't the only one investigating the accident; two federal health agencies and many companies with a stake in the field are digging into the details. Preliminary results of those investigations suggest that a central factor in the tragic events that led to Gelsinger's death is one that has dogged the field from its inception: the difficulty of transferring genes to human cells and getting them expressed.

Wilson, the chief of Penn's clinical team, appeared with co-investigators Mark Batshaw and Steven Raper at a special public meeting at the National Institutes of Health (NIH) in Bethesda, Maryland, on 8 and 9 December to examine what went wrong. He faced members of the Recombinant DNA Advisory Committee (RAC)—a safety group that advises the NIH director—and a special RAC working group headed by geneticist Inder Verma of the Salk Institute in La Jolla, California. With his peers sitting in front of him on an elevated stage and a large audience at his back—including Gelsinger's father, reporters, and photographers—Wilson described in excruciating detail how Gelsinger had died. It was a tense session.

After releasing stacks of clinical data and answering questions for 2 days, however, Wilson and colleagues said that they didn't fully understand what had gone amiss. They reported that the vector they used—a crippled form of adenovirus combined with a gene to control Gelsinger's ammonia metabolism (the gene for ornithine-transcarbamylase, or OTC)—invaded not just the intended target, the liver, but many other organs (see bar graph). This triggered an "activation of innate immunity," the Penn clinicians wrote, followed by a "systemic inflammatory response." Within hours, Gelsinger's temperature shot up to 104.5 degrees Fahrenheit. He went into a coma on the second day and was put on dialysis and then on a ventilator. His lungs filled with fluid. When it became impossible to oxygenate his blood adequately, he died.

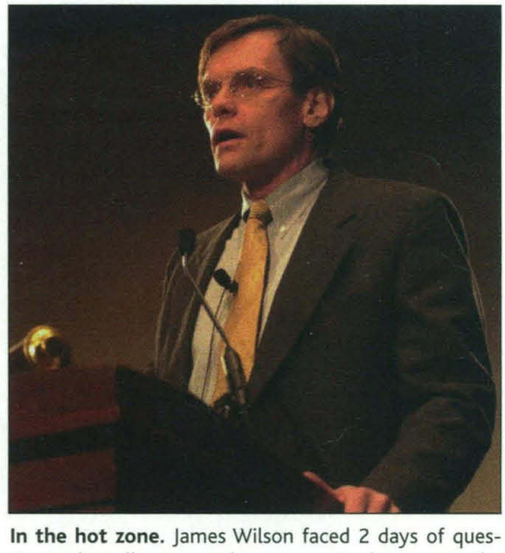


Post-mortem. Traces of adenovirus DNA (E2a) and a curative gene (OTC) it carried turned up in many tissues outside the patient's target organ, the liver.

The Penn team had given Gelsinger a massive dose of the vector—38 trillion virus particles, the highest dose in this 18-patient trial—to try to get enough functioning OTC genes into his liver. But even so, only 1% of the transferred genes reached the target cells. None of the patients in the trial showed significant gene expression.

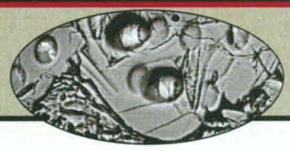
Why weren't the high-dose effects foreseeable, and why were so few genes transferred? Animal trials had indicated a higher transduction rate, but the Penn team doesn't know why the adenovirus vector works less efficiently in humans. As for the toxicity, they suggested that Gelsinger's reaction was an anomaly. At the meeting, Wilson and his colleagues reviewed earlier animal and human data, which they said gave no hint that their dose-escalation study was moving into a lethal range. Other clinicians who spoke at the meeting described "manageable" adenovirus toxicity that they had seen in earlier trials, most of them at lower doses, but Wilson spoke of running into a surprisingly steep "elbow" of toxicity in the dose-response curve.

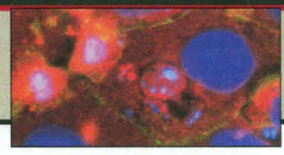
Looking for clues to what happened, the Penn team discovered that Gelsinger's bone marrow was severely depleted of erythroid precursor blood cells—which could not have happened quickly, they felt. To Wilson, it suggested that Gelsinger might have had an undetected genetic condition or a parvovirus infection, either of which might have helped trigger the harsh immune response. Wilson also noted that the vector had been taken up most rapidly by immune cells—"not encouraging" for the efficiency of future trials, he said, because it meant that these cells, not target cells, would be affected first and possibly disseminate the im-

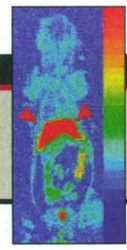


In the hot zone. James Wilson faced 2 days of questioning by colleagues and government advisers over the death of an 18-year-old patient.

SOURCE: (TOP) UNIV. OF PENNSYLVANIA; CREDIT: (BOTTOM) SAM KITTNER







mune response.

Most gene therapists at the meeting agreed that Gelsinger's reaction was unusual. For example, Robert Warren, a clinician at the University of California, San Francisco, said that he had not seen serious toxicity—except in one patient who lost blood pressure—in the more than 40 cancer patients he has treated with adenovirus vector. Ron Crystal of Cornell University's New York Hospital said that he had administered similar vectors 140 times and seen a serious immune reaction only in one cystic fibrosis patient in 1993.

One researcher publicly challenged the notion that Gelsinger's reaction was unusual. Art Beaudet, chair of molecular and human genetics at Baylor College of Medicine in Houston and a member of RAC's special working group, said: "You don't need to evoke anything weird" in this case. Because adenovirus is known to trigger an immune response and because the Penn team kept raising the dose, Beaudet suggested, a sharp immune reaction might not be so strange. Thomas Caskey, a research executive at Merck & Co. of Whitehouse Station, New Jersey, also told *Science* that he thought the Penn trial had been "pushing the edge of the envelope." Beaudet and Caskey are both testing a new, "gutless" adenovirus vector stripped of all native genes, which they say has eliminated most toxic immune responses in animals. It hasn't been used in clinical trials, however.

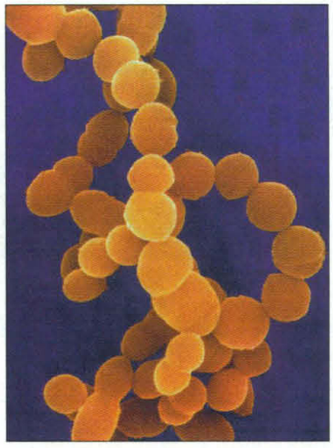
Members of the RAC and the special working group praised the investigators for sharing data and ended the session with mild proposals. Summing up, Verma urged clinicians to adopt a common index for dosing patients and a standard measure of virus particle concentration. These are "obvious" ideas, he said. Others suggested that RAC assemble a database on vectors and their effects; that clinicians screen patients more carefully; and that researchers collect better data on the fate of vectors in the body.

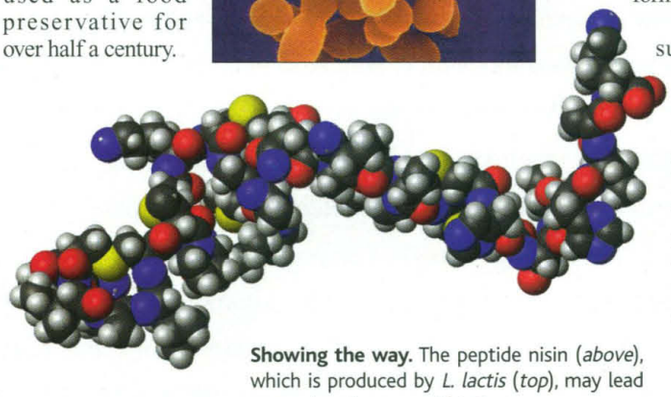
Gelsinger's death "did some damage to gene therapy, and it did some damage to clinical research," a key federal official said when the public meeting was over. The Food and Drug Administration has already announced that it found "deviations" from the protocol in Penn's conduct of the trial, including a decision to treat Gelsinger even though he had an ammonia level before the trial that was 30% to 60% higher than the agreed limit. The FDA is expected to issue a report and possibly a reprimand soon. The RAC and another NIH advisory group are thinking about how to improve the monitoring of gene therapy and will send recommendations to the NIH director for action early next year. **–ELIOT MARSHALL**

MICROBIOLOGY

Promising Antibiotic Candidate Identified

The ever-increasing resistance of pathogenic microbes to antibiotics has raised the specter of a "postantibiotic era" in which doctors are powerless to treat many bacterial infections. Even vancomycin, a longtime antibiotic of last resort, appears to be losing its punch. Now researchers have come up with a possible replacement—one that they say could lead to a whole new generation of antibiotics. It's not a brand-new invention, however. In fact, it has been used as a food preservative for over half a century.





Showing the way. The peptide nisin (*above*), which is produced by *L. lactis* (*top*), may lead researchers to new antibiotics.

The compound, nisin, is a peptide—a small proteinlike molecule—produced by *Lactococcus lactis*, a bacterium that can turn milk sour, to kill its competitors. Microbiologists have known for decades that nisin is an effective killer, but they never knew exactly how it worked. On page 2361, a Dutch-German team provides an answer. They show that the peptide latches onto a molecule on many bacterial cell membranes known as Lipid II—the same target used by vancomycin. The result suggests that nisin, or derivatives of it, could one day replace vancomycin as a broad-range antibiotic. And because nobody has ever found a bug that is resistant to nisin, the researchers hope that nisin and related compounds might trump the problem of bacterial resistance. "This looks like a very significant contribution," says biochemist Norman Hansen of the University of Maryland, College Park.

Nisin is only one of many antimicrobial peptides that have recently caught researchers' interest; others have been isolated from frog skin, insects, and plants, for instance. Most kill bacteria by sticking to and punching a hole in their fatty cell membranes. Some studies suggested that nisin might work the same way. But whereas large quantities of the other peptides are needed to do the job, limiting their usefulness, nisin always stood out because it is effective at concentrations up to 1000 times lower, making it a popular preservative for dairy and many other products. "There has always been this question about why nisin is different," says Tomas Ganz, who studies antimicrobial peptides at the University of California, Los Angeles.

Other work had suggested that might be because nisin has a different mode of action: Like vancomycin, it might bind to Lipid II, which is a precursor of the bacterial cell wall, a tough protective layer that lies outside the membrane. The binding would rob bacteria of their ability to build cell walls, eventually killing them.

The new study, from biochemists Eefjan Breukink and Ben de Kruijff of Utrecht University in the Netherlands, together with colleagues at three other institutions, indicates that both explanations are in fact partially correct. For example, the researchers found that nisin resembles magainin, a peptide antibiotic derived from frogs, in that it kills *Micrococcus flavus* bacteria within a few minutes by forming pores in the cell membrane. But they also found that van-

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