HEMOPHILIA

After a Setback, Gene Therapy Progresses ... Gingerly

Amid all the controversy and allegations over gene therapy, clinical research is continuing, and something close to a success story is emerging

Katherine High and Mark Kay were on a roll. Working independently, the researchers had pulled off a scientific tour de force: In January 1999, each reported using gene therapy to partially correct hemophilia in dogs. By April, the bicoastal duo—High is a hematologist at Children's Hospital of Philadelphia and Kay is a pediatric geneticist at Stanford University—had joined forces and won approval to test the new therapy in humans. In the first stage of clinical trials, they injected a novel gene into the leg muscles of three hemophilia patients. The outcome proved better than either had dared to hope: At a very low dose designed to test safety, not efficacy, the therapy did not harm patients and even showed signs of alleviating disease symptoms. The results, published in the March 2000 issue of *Nature Genetics*, brought a wellspring of hope to hemophilia patients—of which there are 15,000 in the United States alone—and a welcome tonic for a field in which hype has far outstripped payoffs.

Seemingly on their way to the gold, High's and Kay's teams were preparing to up the dose in the next trio of patients and seek approval for a second trial that would inject the novel gene directly into patients' livers. But on 17 September 1999, the death of Jesse Gelsinger in a gene therapy trial hit headlines—and the field—with sobering force (*Science*, 17 December 1999, p. 2244). "We were worried," Kay recalls. "We had no doubt that the field was going to fall under a lot of scrutiny."

Many clinical trials were immediately put on hold; others were cancelled outright. Gelsinger's death, caused by the injection of a novel gene construct into the young man's liver, prompted a spate of investigations that raised questions about everything from the choice of vector to deliver the novel gene, to ethical issues such as patient recruitment, consent forms, and financial conflict of interest. Overall, the tragedy forced the research community into a collective soul search. Although successes had been few and far between, gene therapy practitioners had assumed their research was safe—until now.

"It was a defining moment where people began to say, 'Let's separate the wheat from the chaff here,' " says Society for Gene Therapy president Inder Verma of the Salk Institute for Biological Studies in La Jolla, California. Verma headed a special meeting of the Recombinant DNA Advisory Committee (RAC) in December 1999 to investigate the Gelsinger case.

High and Kay voluntarily lowered the dose they had planned to give the second cohort of patients in the muscle trial. They also postponed seeking approval for the liver trial, which would inject the novel gene into the hepatic artery—the same route of administration used in the Gelsinger trial.

Since the incident, away from the public glare, clinical work in the gene therapy field has quietly continued. Indeed, some of the most encouraging results to date, High and Kay's included, have been reported in this past year. In April 2000, for instance, a group at the Pasteur Institute in Paris published the first unequivocal results showing that gene therapy can treat a rare immune disease called severe combined immunodeficiency (SCID) (*Science*, 28 April 2000, pp. 627, 669). Four months later, a team at M. D. Anderson Cancer Center in Houston reported success using gene therapy in combination with chemotherapy to halt tumor growth in patients with head and neck cancer. Most recently, a group at the University of Pittsburgh used gene therapy to repair a defect in mice with an ailment that mimics Duchenne type muscular dystrophy.

But as High and Kay readily concede, the field has been irrevocably changed by what happened that day at the University of Pennsylvania in Philadelphia and the stringent regulations that have since emerged. "The final rules are still not implemented," says Kay. "But, depending on what happens, clinical trials may become so difficult and expensive that academic centers will not be able to do them." The current environment could deal a hefty blow to a field long plagued by doubt—or simply mark its transition from infancy to maturity.

A deceptively difficult task

High and Kay want to correct hemophilia by giving patients a novel therapeutic gene to make up for a defective one—in this case, a gene that codes for a blood clotting factor. The strategy seems straightforward: Bundle the gene inside a modified virus and allow that vector to ferry the gene inside the patients' cells. Then, if all goes as planned, the

Katherine High: "It was such an obvious idea, transferring genes from one organism to another. But as we used to say in the lab, ideas are cheap."

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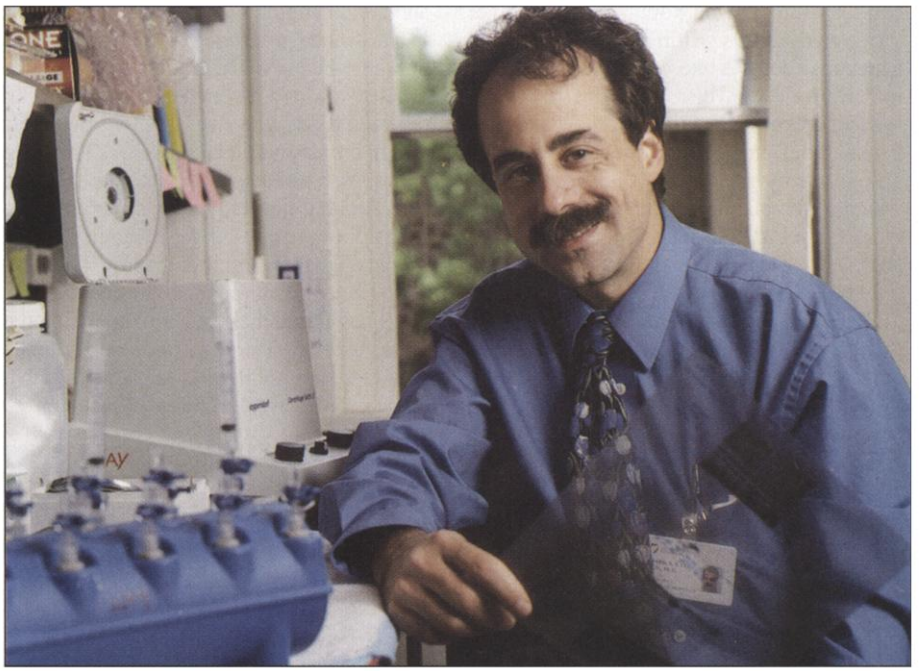
new gene will insert itself into the cells' chromosomes. There, basic cell machinery will switch on the corrective gene and produce the much-needed clotting protein.

But, as High and Kay can attest after almost a decade of trying, the feat is much more elusive than it sounds. Like everybody else in the field, they had to overcome a core—and daunting—problem: how to get enough functioning genes into target cells so they would make sufficient quantities of protein, and how to do so without triggering a severe immune reaction. After numerous fits and starts, High and Kay are now using a promising new viral vector, but it still has limitations: It can't yet carry the full-length gene needed to correct one common form of hemophilia. And overall, no gene therapy treatment has yet reached the market for any disease. Through the course of their studies, High and Kay hooked up with a company that hopes to commercialize their treatment, but such a product is years away, they caution. In short, although High and Kay are now considered two of the stars of gene therapy, their decade-long struggle shows just how tough life can be on this new medical frontier.

High, now director of research in the hematology division at Children's Hospital, never expected to end up pursuing gene therapy—or in the middle of one of the most controversial fields in medicine. In fact, she dreamed of working as a bench chemist. But in the late 1970s, she got hooked on medicine in general and hemophilia in particular during a stint with pathologist and coagulation expert Kenneth Brinkhous and his famed blood coagulation group at the University of North Carolina, Chapel Hill.

The group's main focus was hemophilia, an X chromosome–linked disease that afflicts about 1 in every 5000 people, mostly males. The disease is characterized by the lack of at least one of a family of key enzymes that aid in blood clotting. Two of the most prominent are called Factor VIII, which is the culprit in hemophilia A, and Factor IX, which when defective causes hemophilia B, the less prevalent of the two disease forms. The sickest patients suffer uncontrollable bleeding episodes and debilitating joint damage.

Then, as now, clinicians had few treatment options for hemophilia: mainly giving patients injectable concentrates of a clotting factor derived from blood plasma (now, by recombinant means); or, in developing countries, where most hemophiliacs don't live beyond their 20s, simple bed rest and ice. Patients with a severe form of the disease—defined as making less than 1% of the normal amount of either clotting factor—have to inject themselves with blood factor proteins up to three times a week at a cost approaching $100,000 a year. Such injections promote clotting and temporarily relieve joint pain, but they have had ugly consequences: More than 90% of adult hemophiliacs are now infected with hepatitis C or HIV from contaminated blood products. Patients with a more moderate form of the disease—defined as having 1% to 5% of normal levels of the enzyme—live a significantly easier life with far fewer injections.



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Mark Kay: "I wasn't worried [from] the standpoint of having a safety problem. I was more worried about what the environment and the perception might be."

Thus, the Holy Grail for any hemophilia gene therapist is to boost the active level of enzymes above the benchmark 1%. That fairly lax requirement is one reason why a handful of intrepid researchers venturing into gene therapy in the early 1990s picked hemophilia as their target. Another reason is that the protein can make its way into the bloodstream, where it is needed, when the gene is expressed in any one of a multitude of cell types, unlike, say, cystic fibrosis, in which the gene must be expressed in the lungs or surrounding tissue.

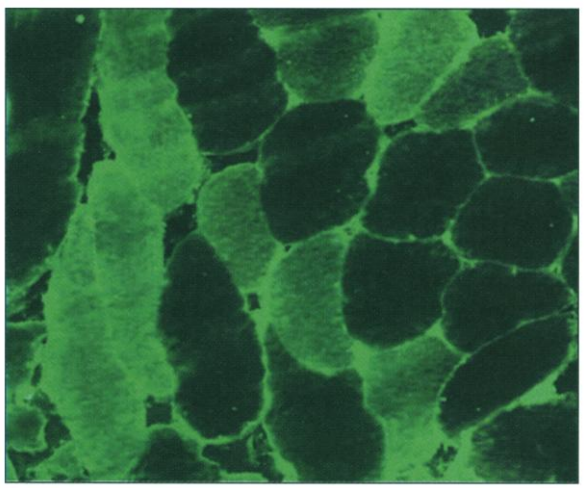
But first investigators had to find and characterize the human genes for Factor VIII and Factor IX—a feat pulled off by researchers including George Brownlee and colleagues at Oxford University in the mid-1980s and Darrel Stafford at Chapel Hill. Hemophilia researchers, including High, spent the next 5 years determining how defects in those genes influence disease severity. "This was a fertile time for expressing clotting factors and getting large amounts of them to study," High recalls. Specifically, High studied how alterations in the structure of the protein affect its function as a blood clotting enzyme. But her group needed animal models in which they could better study the disease and its treatments.

So in 1989, High and postdoc Jim Evans identified, cloned, and characterized the Factor IX gene defect that causes hemophilia B in a colony of dogs born with the illness. Canines are the animal model of choice because of their size and similarity to humans. But dogs are expensive to house and relatively hard to work with. To create a more malleable mouse model, three groups led by Stafford at Chapel Hill, Verma at Salk, and Erlinda Maria Gordon at the University of Southern California in Los Angeles, knocked out the gene for Factor IX in a strain of mice in the early 1990s. Haig Kazazian, currently chair of genetics at Penn, did the same for Factor VIII. With this work, hemophilia researchers had a gamut of organisms to work with, from cells to rodents to dogs. "It is a model that a lot of gene therapy ought to copy, if it could," says gene therapist Savio Woo of Mount Sinai School of Medicine in New York City.

Early in 1991, High and colleagues decided to take the plunge into gene therapy. "It was such an obvious idea, transferring genes from one organism to another," High explains. "But as we used to say in the lab, ideas are cheap." And often they don't work, High soon found out. When trying gene transfer experiments in animals, her Chapel Hill team quickly ran into the roadblocks that had stymied other fledgling gene therapists: namely, the vectors. For years, researchers could not coax the contemporary virus vectors to shuttle Factor IX genes into

cells in culture. One popular vector of the day, retroviruses, didn't deliver enough genes into cells to eke out even 1% of normal Factor IX levels. The other available vector, adenoviruses, had its own drawbacks, chief among them that the immune system easily recognizes the virus vector, which in its unaltered state causes the common cold. Host cells harboring adenoviruses and their corrective genes are quickly pitched out of the body.

On a national front, meanwhile, gene therapy was gaining credibility. After lengthy debates on safety and ethical issues, W. French Anderson, then at the National Institutes of Health (NIH), and colleagues in 1990 had won approval from the RAC to conduct the first human gene therapy trial in the United States. In September, with reporters and photographers on hand to record the event, Anderson and his colleagues injected a corrective gene into a 4-year-old girl with SCID. Trials to treat various cancers followed 5 months later.



Signs of success. In clinical trials, High and Kay injected adeno-associated virus carrying a corrective gene for hemophilia into the leg muscles of several patients. As hoped, the cell's machinery switched on the gene that codes for blood clotting factor IX. Fibers expressing the clotting factor appear green.

CREDIT: MARK A. KAY AND ROLAND W. HERZOG/THE CHILDREN'S HOSPITAL OF PHILADELPHIA AND UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

A new vector offers hope

A year after Anderson's pioneering experiment, High moved to Penn, where she could devote herself entirely to lab work. She set up shop in the pediatrics department of the affiliated Children's Hospital. At Penn, officials were aggressively building the Institute for Human Gene Therapy, now the largest in the country. James Wilson, who later led the team of doctors that treated Gelsinger, was hired in 1993 to head it.

About the time High made her move, a hot new virus vector, known as adeno-associated virus or AAV, made its debut. High and many others were right on it—including Kay on the other side of the country. First developed and patented for use as a biological vector by virologists Barry Carter, then at NIH, and Nicholas Muzyczka of the University of Florida, Gainesville, the novel vector looked like the much-needed shot in the arm for the disheartened field. The vector, in essence, is a core of viral DNA shrouded in a protein coat. Related to adenovirus in name only, AAV doesn't cause any disease in humans or other mammals. The virus simply enters cells and homes in on chromosome 19. There, the strand of viral DNA inserts itself and becomes a permanent part of the host cell's chromosome.

Given this mode of integration, researchers hoped that this new vector, unlike adenovirus, might be able to avoid detection and annihilation by the host immune system. What's more, it seemed to be able to target nonreproducing cells. But again, there were problems. Many researchers soon found that they could not coax the virus to grow in culture in the lab. Nor could they shoehorn large genes, such as Factor VIII, into the viral capsule. And once loaded with smaller corrective genes, the virus no longer integrated into its predictable spot on chromosome 19 but inserted randomly throughout the genome.

A few found their way around these problems. One was viral guru Jude Samulski, now at Chapel Hill, who in the early 1990s pioneered the use of AAV as a gene-delivery vehicle. Samulski encouraged High and supplied her with the biological materials she needed to make the crucial vectors. With Samulski's help, High succeeded in splicing the gene for Factor IX, which is shorter than that for Factor VIII, into AAV.

In key experiments in 1997, High and postdoc Roland Herzog teamed up with Wilson. The team injected AAV carrying human Factor IX genes into the leg muscles of mice; after the gene integrated into muscle cell chromosomes, the rodents steadily and stably churned out therapeutic levels of Factor IX. The following year, High was able to use AAV, loaded with human Factor IX, to correct hemophilia in Stafford's genetically altered mice by injections into either rodents' leg muscles or livers.

Finally in January 1999, High, Herzog, and Tim Nichols, also of Chapel Hill, reported in *Nature Medicine* that they had partially corrected hemophilia B in a dog colony. To do so, they injected AAV, laden with canine Factor IX, into the animals' leg muscles. The paper ran back to back with an equally eye-catching report. Kay's group at Stanford, in collaboration with Richard Snyder, then at Somatix Therapy Corp. in Alameda, California (now owned by Cell Genysis), had independently engineered its own version of AAV carrying the gene for Factor IX. The West Coast team had pumped the vector directly into liver veins of hemophiliac mice and dogs obtained from Nichols. The liver procedure, although more invasive and therefore more risky than muscle injection, proved to be slightly more efficacious. In both procedures, the treated dogs produced at least 1% of normal blood levels of Factor IX. Kay's liver protocol, however, needed 10-fold fewer viruses to do the trick, in part because of stronger liver-specific promoters that drive the gene harder.

"These were very promising studies," says Anderson, who notes that at that time, no one had achieved such high levels of expression by injecting a new gene directly into muscle tissue.

From competition to collaboration

Unlike High, hemophilia wasn't even Kay's area of expertise—it was gene therapy instead that drew him into the field. As an M.D.-Ph.D. student at Case Western Reserve University in Cleveland in the early 1980s, Kay was struck by the potential of this budding field. Admittedly naïve, Kay initially feared the field would pass him by. The concept seemed so simple, "I figured by the time I'd finished medical school, residency, and my fellowship, all the interesting diseases would already be cured," he recalls.

That was hardly the case. By the time Kay graduated from Case in 1987, Anderson and other gene therapy pioneers were still wrestling with uncooperative vectors and tough regulatory hurdles that seemed to be getting tougher, as members of the RAC battled with Anderson and each other. Kay got his chance to witness gene therapy experiments firsthand in 1989, when he moved to Baylor College of Medicine in Houston, Texas. As he completed his pediatric genetics residency in the clinic, he also worked at the bench with molecular biologist Woo, who was then beginning to dabble in gene therapy.

Kay wanted to use those nascent tools to help the children he saw in the clinic, most of whom were stricken with so-called inborn errors of metabolism. These diseases often involve rare genetic defects in various crucial liver enzymes—defects that cause devastating, if not fatal, consequences. "We could make the diagnoses, but we were really horrible at trying to develop efficacious therapy," Kay recalls. "I realized that the chances of treating these diseases with anything other than gene therapy [were] pretty low."

Kay started working on hemophilia in the hope that any gene therapy techniques he devised could later be used for other liver-

based disorders. By the end of his Baylor stint, Kay had been able to partially correct the defect in hemophiliac dogs using a retrovirus that carried Factor IX. But the procedure itself was draconian and "not something that you could do to people on a wide scale," says Kay. Because retroviruses can only target dividing cells, injecting the vector directly into the body failed to get anything more than a negligible amount of corrective genes into liver cells. Kay's team had to remove two-thirds of an animal's liver, prod the cells to divide in culture, and then infuse the retrovirus vector carrying the Factor IX gene into the vein that runs into the liver.

Despite the clinical impracticality, Kay published his work in 1993 as a "proof of principle" (*Science*, 1 October 1993, p. 29). Such obstacles gave Kay pause, however. "You solved one problem, and then you'd get another you did not anticipate," Kay recalls. "I really thought hard about whether I should work on gene therapy." At the same time, Kay and other gene therapists were confronting an increasingly skeptical research community. After repeated failures and slow progress, a 1995 report commissioned by then–NIH director Harold Varmus essentially warned the community to turn down the hype.

Kay decided to stick with gene therapy, lightening his patient load and devoting most of his time to looking for other vectors and strategies to improve gene transfer into human cells. "I realized that to be effective, I couldn't be doing a little bit of everything," says Kay, who by 1993 had moved to the University of Washington, Seattle. Kay's move came on the heels of High's relocation to Penn. And like High, Kay soon began working with AAV, trying to engineer a construct to treat hemophilia in a mouse model. Because of his bent toward liver diseases, Kay worked on liver routes of delivery instead of methods with muscle cells, enlisting the help of Snyder at Somatix to provide him with a steady supply of AAV.

Almost a decade of effort paid off in 1997, when Kay and colleagues reported in *Nature Genetics* that they had provided normal mice with curative levels of human Factor IX via one injection of genetically altered AAV into the rodents' liver veins. Only then, says Kay, did "I realize that gene therapy really would work in people."

Kay and postdoc Hiroyuki Nakai spent the next 2 years trying to extend this work to dogs. In January 1999, as "friendly competitors," Kay and High published their dueling *Nature Medicine* papers showing the partial correction of hemophilia (up to 1% of normal protein levels) in dogs. The feat placed them well ahead of their colleagues and competitors such as Salk's Verma, who in 1998 also used AAV—injected into the liver—to correct hemophilia in mice lacking Factor IX. "Up until this point, [corrective] Factor IX genes could be expressed but not enough to make therapeutic amounts of protein," Verma says.

Kay and High, who often sat together trading notes at NIH meetings on hemophilia gene therapy, soon decided to collaborate and move the work into humans, fusing her expertise in hemophilia with Kay's flair for manipulating vectors—a winning combination, says Anderson. High recalls saying to herself, "Well, I could stay funded for the next 20 years just doing mouse and dog experiments, and it would be a lot less grief for me. But sooner or later I have to ask, 'Is this going to work in people?' "

Into humans

The deal was set. High would take the lead on delivering the corrective gene via muscles —and write up the necessary documents for Food and Drug Administration (FDA) approval in that tissue—while Kay would do the same for liver approaches. Avigen, a biotech company in Alameda, California, that High had been working with, would make the AAV vectors for both and help fund the trials. In this arrangement, the researchers sit on Avigen's scientific advisory board and are compensated for their time and expertise. To avoid the appearance of any conflict of interest, the two do not directly participate in recruiting patients, gaining informed consent, or treating patients in the trials. The regulatory bodies bought it. By April 1999, the pair passed through biosafety committee and internal review by boards at both Stanford, where Kay is now director of the program in human gene therapy, and Children's Hospital; initial review by the RAC; and then ultimate approval by the FDA for safety trials.

Royal blood. Queen Victoria's family was plagued by hemophilia, an X chromosome–linked disease that affects mostly males.

Kay and High thought the biggest risk lay in a quirk of hemophilia. Individuals with certain forms of hemophilia—the type caused by large deletions of genetic material as opposed to simple misspelled nucleotides —do not produce any clotting factors at all; thus, the immune system has not had a chance to develop a "tolerance" to the otherwise native proteins. High and Kay worried that if they successfully introduced a gene for the clotting factor into patients with large gene deletions, thereby providing them with a steady supply of protein, the patients' immune systems might consider the protein to be foreign and make antibodies to destroy it. Not only would gene therapy be unsuccessful, but patients' lives might be endangered if, during a later bleeding episode, they produced antibodies to the clotting enzymes administered to save them.

For these and other safety reasons, Kay and High decided to start with muscle instead of liver injections. Even though AAV takes 6 to 12 weeks to settle into a nesting site within the cell nucleus, the gene usually does not stray far from the site of injection —in other words, if the vector were injected into the muscle, it would stay there. "If you have some unanticipated untoward effect, you can go back and resect the muscle," High notes. "Once you go into the liver, that's it. You are there."

To hedge their bets further, High and Kay selected only patients with misspelling mutations. Those may cause the gene to produce a faulty blood clotting protein, but a protein nonetheless. That meant that all patients in the trial would likely have been exposed to inactive blood clotting factors. The duo won FDA approval for their muscle trial—the first gene therapy trial ever to inject AAV.

High watched anxiously from the side of the treatment room in June 1999, when hematologist Catherine Manno, who led the clinical team at Children's Hospital, injected the first patient with genetically altered AAV. To their relief, the procedure went without a hitch. As the team reported in the March 2000 issue of *Nature Genetics*, at the initial, suboptimal dose meant only to detect obvious safety problems, the first three patients, aged 23 through 67, showed no apparent toxicity. Even more encouraging, within 12 weeks after the injection, the team detected normal Factor IX genes—and the actual protein itself—in biopsies taken from the patients' legs. That meant that the gene had been incorporated into muscle cells and then produced its protein. The presence of Factor IX in the bloodstream suggested

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that the protein had successfully crossed from tissue to its target destination. To date, none of the three patients has produced any antibodies to fight off the protein.

What's more, High and Kay reported, patients fared even better than animal studies would have predicted: Even at low doses, one of the three patients showed a boost in circulating levels of Factor IX—one even topped the benchmark 1%. Two of the three patients also reported needing significantly fewer therapeutic protein injections to treat and prevent bleeding episodes.

To Anderson, now at the University of Southern California, the results were "not a matter of excitement, but a matter of relief." If gene therapy doesn't work for hemophilia, he says, it is unlikely to succeed for most other diseases. An ever-cautious High will only say she was "surprised and pleased" at the apparent, although preliminary, success.

Although the early results appear positive, Salk's Verma also warns against overoptimism. Because the patients in the study did not yet make enough protein to cure their disease, they also did not make enough to test whether the added protein will trigger the production of anti–Factor IX antibodies. "It's a double-edged sword," says Verma.

The Gelsinger case

Buoyed by their preliminary success, High and Kay moved to collect more data. But, just as the team was getting ready to inject the next three patients with a slightly higher dose and to propose a second trial, Jesse Gelsinger died. The news hit hard. The young man was being treated for an entirely different disease: a deficiency in a liver enzyme called ornithine transcarbamylase that's needed to remove ammonia from the blood. The Penn team was also using a different vector—adenovirus—one that Kay and High had abandoned. But there was one similarity: High and Kay were proposing to introduce their more benign vector via the exact same entry route that the Penn team had used: direct infusion into the main liver artery.

FDA soon halted all trials at Penn's Institute for Human Gene Therapy and stopped several other human studies using adenovirus vectors (as opposed to AAV). Although High and Kay's trial was not directly affected, all gene therapy fell under intense scrutiny.

Without any prodding, High and Kay immediately began to review their animal and human data to decide how or whether to go forward. "I think it is really important, number one, that safety issues are addressed," says Kay. "There has been some debate by members of the gene therapy community that if the rules had been followed previously, this might not have happened," he says, referring to the death at Penn.

The pair decided to lower the next dosing regimen to a half-log increment and sent a letter to the FDA requesting permission to modify their trial. Kay and High had also planned to present their proposed liver trial to the RAC for discussion at its December 1999 meeting but postponed the review until the following March. "I wasn't worried [from] the standpoint of having a safety problem," Kay says. "I was more worried about what the environment and the perception would be."

It proved to be a wise decision. At a packed 2-day meeting conducted under the glare of television cameras, it became clear that both the adenovirus vector and the route of administration were suspect. Scrutiny continued at the next RAC meeting on 9 March, when Kay and Bert Glader, the Stanford physician who would head the clinical trials, presented their proposal to use AAV, injected into the liver artery, to carry a corrective gene into hemophilia patients. It passed muster. The RAC approved the proposal, and the trial now sits before the FDA awaiting the ultimate nod.

As the researchers wait, the muscle trial continues. On the advice of FDA, Manno has amended the consent form for clinical trials to mention the Gelsinger death and the risks of gene therapy. The middose crop of patients is doing well, Kay and High reported at an American Society of Hematology meeting in San Francisco in November 2000. One patient achieved the 1% benchmark and reported a reduction in self-administration of clotting factor. The other two, however, did not reach that benchmark. "We're still looking for a dose where every subject gets a result over 1%," says High. The team recently increased the dose by another half-log in three more patients.

> **"It was a defining moment where people began to say, 'Let's separate the wheat from the chaff here.'"**
>
> **—Inder Verma**

High and Kay will likely have to meet even more stringent requirements in the liver trial. Over the past year, the RAC proposed new reporting and monitoring requirements to enable them to track adverse events. Among other things, these rules call for an independent monitor to check that data are being collected and reported properly. Hiring such an expert can add $100,000 to the already hefty price of clinical trials. Kay says that every day he spends an increasing amount of time complying with these rules and worries about the effect of such costs and paperwork on the field.

Despite the expense, however, the pharmaceutically minded are convinced the investment will payoff. Avigen announced in November that it had entered a partnership with pharmaceutical giant Bayer Corp., headquartered in Leverkusen, Germany. Bayer, with a long interest in hemophilia drugs, plunked down $60 million to help conduct and finance phase II and phase III clinical trials with Avigen's Factor IX–laden AAV vector, dubbed Coagulin-B. In exchange, Bayer will hold regulatory licenses of the drug worldwide and receive royalties from its sales.

Both High and Kay say the Gelsinger tragedy has changed their working lives. "At this point, the field is not something to go into if you want to labor in obscurity," High remarks. "It's a highly visible field because of public, commercial, and political interest. That creates a great deal of pressure."

But, having spent years treating patients, they also believe the potential payoff is well worth the pressure. Indeed, Kay remains as optimistic as he was in medical school. Says Kay: "We are starting to see evidence of success and to really appreciate the potential of gene therapy for the entire field of medicine."

–TRISHA GURA

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CREDIT: SAM KITTNER

Under scrutiny. The death of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania prompted a spate of investigations and hearings, including the December 1999 RAC meeting where James Wilson, head of Penn's Institute for Human Gene Therapy, testified.