Gene therapy: cursed or inching towards credibility?

Can gene therapy ever live down its setbacks and live up to its initial promise? A chastened but determined group of pioneers believes it can, and they are pointing to a new generation of products to back up that claim. Malorye A. Branca investigates.

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Future gene therapy candidate? Nine-year-old child with Crigler-Najjar syndrome, a genetic disease that causes elevated bilirubin levels, sleeps under UV lights every night.

On February 9 the US Department of Justice announced a civil settlement in the government's case related to Jesse Gelsinger's death during a gene therapy trial at the University of Pennsylvania in 1999 (see News in Brief, p 515). Gelsinger, just 18 when he died, was not the first person to die while receiving experimental treatment, but both the circumstances of his death and the anxiety many people feel about genetic manipulation in general brought the case extraordinary attention. "There was a definite negative effect on the entire field [after Gelsinger's death], as we all paused to reconsider what we were doing," says Richard Gregory, head of research at Cambridge, Massachusetts' Genzyme.

This, plus the latest round of interruptions of some gene therapy trials, less than a year after a high profile French trial was resumed (**Box 1**), has put this once promising field back on the hot seat, just when researchers and companies felt they were finally making some progress. Will this latest round of negative publicity put gene therapy back in the doldrums or can an approval, believed by some to be coming in the next 2–3 years, finally bring some commercial success to the sector?

Heavy baggage

Nowhere in biotechnology has the promise been more tantalizing and the failures more devastating than in gene therapy. The idea that scientists could treat the errors in our very DNA initially gave new hope to many, particularly the desperate parents of children with fatal inherited disorders such as cystic fibrosis or muscular dystrophy. Those dreams have been dashed, as repeated set backs have forced investigators to completely rethink the best ways to first move their brave new therapies into medical practice. Now that one of the bleakest episodes in gene therapy's history has finally ended, at least officially, have we entered the dawn of better gene-based therapies? The answer seems to be yes, if the latest wave of products fulfill expectations.

Most agree a pause for reflection was warranted, and that the result has been a much better understanding of the underlying science. But some investigators feel the new regulatory restrictions go overboard, unduly shackling those already using appropriate caution, by adding steps to an already difficult process.

Ironically, although Paul Gelsinger, Jesse's father, does believe the technology was hyped prematurely, he doesn't blame gene therapy for his son's death. "The problem wasn't gene therapy," he says. Rather he faults certain individuals and the system (**Box 2**). Others saw it differently, however, and gene therapy was branded as an unusually risky field within the already volatile biotechnology sector. Some companies shifted their focus to new fields, or recast their work.

"Because gene therapy has such a nasty reputation, people tried to rename it or call it 'new and improved' to free themselves of the stigma," says Michael Zasloff, an analyst with Ferris, Baker Watts of Washington, DC. "That may fool the public, but the market sees through it," he says. Wherever genetic manipulation is involved, no matter for how long or where in the body, investors typically treat it like gene therapy, despite what the product's developers may say.

Safety and efficacy

It is not just safety problems that have dogged gene therapy, efficacy has been much harder to achieve than expected.

Katherine High, of Children's Hospital of Philadelphia, has experienced the field's ups and downs from the front row. Along with Mark Kay's group at Stanford University and scientists at Alameda, California–based Avigen, she has spent years moving a gene therapy for hemophilia through to human studies. Mouse studies seemed promising and the dog studies were remarkable—with animals producing adequate levels of Factor IX for more than five years. Then, in the human trials, the therapy seemed to be working well in at least one patient. But that quickly proved to be an illusion. Five weeks later, the patient's Factor IX levels started dropping and quickly reached baseline.

"I have to admit, at first I was devastated. I couldn't believe it didn't last," High says. Someone from Avigen reminded her to "think how the patient feels. For four weeks, he touched the rainbow." The bottom line is that it has been extraordinarily difficult to get sustained delivery of any gene. Many diseases that originally seemed likely targets have also turned out to be devilishly tough. Cystic fibrosis, for example, was one of the first stops for gene therapy, and

many trials have been carried out by companies including Genzyme. "The CF lung is full of mucus and things like proteases that are hostile to vectors," Gregory says.

As a result, candidate gene therapies for genetic diseases are dropping like flies. Avigen recently announced it is refocusing entirely, moving into small molecule therapeutics and exploring options for keeping alive its gene therapy programs, which include the hemophilia treatment and one for Parkinson disease. "It has just been very tough on the business side," says Avigen's Glenn Pierce. "The timeline is long, and the hurdles are bigger than expected." Strasbourg, France's Transgene also completely abandoned 'real' gene therapy this year, and will now concentrate on its vaccine business. The company's Duchenne/Becker's muscular dystrophy program will continue through support from the French Association against Muscular Dystrophy. Finally, Targeted Genetics recently announced it is ceasing work in cystic fibrosis. Early results from the company's latest phase 2 trial—the largest gene therapy trial ever conducted in this indication—did not confirm earlier encouraging results.

The challenge still is getting enough gene expressed for a sufficient span of time. "The other sad or amusing thing was the gradual discovery of how much the immune system matters here," says Doug Jolly, a gene therapy pioneer and now president and COO of Advantagene of Encinitas, California. An immune response is probably what derailed Avigen's hemophilia treatment, and it is almost certainly what led to Jesse Gelsinger's death.

Miracle cures for genetic diseases are hard to deliver. Experts are still optimistic they will come, but the work on these conditions is now largely confined to academia and other research sponsored by nonprofits. Genzyme may be the one exception here, because it has a long history in the field and a good reason to stay in it. The company launched its first gene therapy trial (for cystic fibrosis) in 1992. It has yet to see a payoff from that work, but in the meantime Genzyme has built a major franchise around protein replacement treatment for the major form of Gaucher disease. That treatment, Cerezyme, is remarkably effectively, but patients with rarer forms of this condition are still incurable. "We are committed to serving all of these patients," says Gregory. If a technology exists that will help more Gaucher patients, or improve upon what Genzyme already has, the company wants to be the first to get it working. As a result, the company is investigating gene therapies for these alternative forms of Gaucher.

Soberly optimistic

Those who've been in the field a while are philosophical about the problems. "We've finally been doing this long enough that bad things are cropping up," says Gregory. Jolly, meanwhile, likes to point out that although trials began in 1990, it took longer for industry to get really involved. "We've only been doing serious drug development in this field for about

Box 1 On the SCIDS

Gene therapy's big worry has always been that a genetic payload could integrate into the host genome in a trouble spot, where it would cause other diseases or even alter a patient's germline. That concern now seems to have been validated by a series of events in France that have put gene therapy's one successful treatment at risk.

The work of Alain Fisher and Marina Cavazzanna-Calvo's group at Necker Hospital was initially hailed as a stunning achievement, when in 2000 they reported successfully treating X-linked severe combined immunodeficiency (SCID) in infants using retrovirus-based gene therapy. It was called the first real validation of the field. But that victory was marred just a couple of years later, when one of the boys developed T-cell leukemia. Soon after the first case was discovered, another child developed cancer, and then another. One of the three boys died from leukemia last year.

As these developments unfolded, SCID trials around the world were first stopped, then restarted, then stopped again. The FDA also held a special meeting in mid-March of this year to review the problem.

Because X-SCID leads to early death if untreated, the consensus so far is that gene therapy should be considered only in children for whom there are no other treatment options. "It's still a wonderful success, but with very nasty possible side effects," says Advantagene's Douglas Jolly.

In the first two cases, the cancer was triggered in the SCID kids after the retrovirus inserted near the LMO2 oncogene promoter. Something similar occurred in the third case, although a different oncogene was involved. Having reviewed the SCID cases, experts believe this side effect is caused by the very gene being treated in the French trial, because this effect has not been seen in other trials.

Table 1 Selected company-sponsored gene therapy trials

Company/location	Indication/treatment site	Product/gene	Vector	Clinical trial phase
Corautus Genetics Atlanta, Georgia	Severe angina/heart muscle	Vascular endothelial growth factor (VEGF) 2	Naked plasmid DNA	2b
Genzyme Cambridge, Massachusetts	Peripheral arterial disease/legs	*HIF-1*α (an engineered form of the hypoxia-inducible factor 1 gene)	Adenovirus type 2	2b
GenVec Gaithersburg, Maryland	Severe coronary artery disease, angina/ coronary arteries	BIOBYPASS/*VEGF121* (proprietary form of VEGF)	Adenovirus	2b
	Pancreatic cancer/tumor	TNFerade/tumor necrosis factor-α (TNFα)	Adenovirus	2
	Age-related macular degeneration/eye	Pigment epithelium-derived factor (PEDF)	Adenovirus	1
Introgen Austin, Texas	Solid tumors/head and neck, lung, breast, esophagus, prostate, brain, pelvis	ADVEXIN/*p53*	Adenovirus	1–3
	Solid tumors/various	INGN 241/*mda7* (encodes IL24)	Adenovirus	1–2
	Solid tumors/lung	INGN 401/*FUS1* (a tumor suppressor gene)	Nanoparticle	1
Targeted Genetics Seattle, Washington	Rheumatoid arthritis/joints	tgAAC94/TNFα	Adeno-associated virus (AAV)	1

12 years," he says, pointing to the fabled 20 years it took monoclonal antibody developers to get it right.

Important lessons have been learned, not just about side effects, but also about efficacy.

"One rule is 'Use vectors locally, before you try them systemically'" says High. The realization that different organs have different side-effect profiles to the same vector has also been critical, reinforcing the importance of vector choice and route of administration. Finally, the explosion in knowledge about certain gene targets has been an unexpected boon. New research on angiogenesis and cancer, in particular, has revealed many attractive gene therapy targets. The result is a nice little wave of progress, albeit in more complicated diseases (**Table 1**). Here the challenge will be finding strong end points to measure the therapies against.

As Stephen Dunn of Boca Raton, Florida, securities firm Dawson James sums it up, the issue now is "Right vector? Right gene? Right target?" That's a much different proposition than curing all genetic diseases with one magic vector, but it's also a plan that is much more attractive to investors.

"Do I like the new crop of gene therapies more than the old? Absolutely," says Zasloff. Treating something locally and transiently with a gene therapy is much less risky than permanently altering gene expression. Even better, from the investor's standpoint, these therapies are targeting more typical markets—conditions such as cancer, cardiovascular disease and rheumatoid arthritis.

No one expects the floodgates to burst open soon, but there is widespread confidence that within the next 2–3 years, a gene therapy will be approved in the US. Others should follow, one by one. "Gene therapy's first successes will be in something localized like solid tumors or eye diseases," says Dunn. Work on new vectors will continue. Already, more research is going into the adeno-associated virus, lentivirus and nonviral vectors. High expect major progress on the vector front within the next ten years. Others agree. "In about 15 years, I like to think there will be several gene therapies hitting the market at once," says Gregory. Although he cautions that if there is another major set back like the one at the University of Pennsylvania, "I can't predict what the effect will be."

The first gene therapy approved in the US will most likely be Austin, Texas–based Introgen's Advexin, which delivers normally functioning p53 to cells. Currently in late phase trials for head and neck, non-small-cell lung and breast cancer, Advexin is also in development as a mouthwash to treat precancerous lesions. The most intriguing thing about this treatment is how safe it appears to be. "These are highly specific, minimally toxic and very targeted products," says Introgen's president and CEO David G. Nance, who points out that the US Food and Drug Administration has approved trials of Advexin even in precancers. He adds that the company has tested its gene therapies in over 700 patients, and never had a trial stopped or put on hold. Introgen, which has several products in development, thus epitomizes the new gene therapy company. Its products are used transiently, tested in combination with other treatments, and locally delivered—Advexin can even be applied directly to a tumor during surgery.

Once one or more gene therapies reach approval in the US, experts believe the big pharmaceutical companies will again start setting up partnerships in the sector. Major players such as Schering Plough of Kenilworth, New Jersey, and Novartis of Basel showed intense interest in gene therapy early on, but have all but abandoned the field over the last few years.

Chinese checkmate

A wild card here is China's bold move into this field. In 2003 the first gene therapy product was approved in that country, much to many people's surprise. Probably most surprised were the management at Introgen, whose lead product is quite similar to the Chinese product—Shenzhen SiBiono GenTech's recombinant Ad-p53 for head and neck squamous cell carcinoma (see *Nat. Biotechnol.* **22**, 3, 2004).

Dunn sees the Chinese connection as important. China is apparently positioning itself as a leader in the field, and hopes to attract medical tourists from afar with breakthrough therapies not available at home. Shenzhen SiBiono claims that about 400 Westerners have already visited China to receive the company's treatment. "Find a Chinese partner," is Dunn's advice to gene therapy companies. Everyone in the field is already watching the developments in China closely. Introgen has chosen to file patents there judiciously, and try to work the political scene. It helps that some of the company's Chinese patents have already been issued. "But we saw what happened to Pfizer," says Nance. "They marched in with a strong patent for Viagra, and got nothing."

Advexin is so similar to Shenzhen SiBiono's product that if the Chinese seek to commercialize their product in the US, "It would be an issue," says an Introgen spokesperson. All the more reason for them to hope they get their US approvals soon and to keep an eye on the East.

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Box 2 A final reckoning in Gelsinger case

Just over five years ago Jesse Gelsinger went to the University of Pennsylvania's Institute of Human Gene Therapy in Philadelphia to take part in a trial aimed at treating inborn ornithine transcarbamylase deficiency. But four days after he received the therapy, Gelsinger died of massive organ failure, apparently sparked by an immune reaction to the adenoviral vector used.

In February of this year, the Department of Justice (DOJ) announced the final civil settlement in the case. The University of Pennsylvania and Children's National Medical Center each agreed to pay more than $500,000 to the government. Both institutions have also been obliged to shore up patient safety procedures. Clinical research restrictions were placed on the three investigators involved—Penn's James Wilson and Steven Raper, and Mark Batshaw, a former Penn doctor and now chief academic officer at Children's National Medical Center. Neither the scientists nor the institutions named admit to any of the government's allegations.

Jesse's father, Paul Gelsinger, is now vice president of Citizens for Responsible Care and Research. He says the settlement does not go far enough. Gelsinger maintains that Wilson's industry ties played a role, that the Gelsingers were repeatedly misled throughout the ordeal and that the FDA should have stopped the trial earlier. "This judgment lets everyone off the hook," he says.

David Hoffman, the US attorney general who prosecuted the case, says the DOJ, FDA, and NIH all approved the final settlement, and that it should serve as a lesson to investigators everywhere, "To have the sense to always view subjects as people, not just 'participants.'"