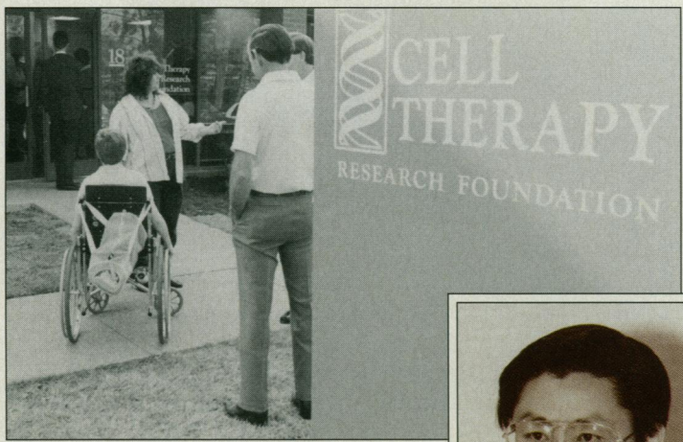
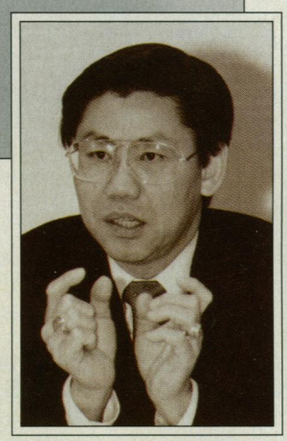
Cell-Transplant Results Under Fire

Peter Law's muscular dystrophy cell-transplant results are so much better than anyone else's that his colleagues are suspicious. To top it off, the FDA is investigating his private research foundation

Here's a researcher's dream. There's a genetic disease, progressive and invariably fatal, which strikes youngsters. You've worked for years, developing what you think is a genetic cure. At an international meeting—the first devoted to your kind of therapy—you present your data from the largest human test of this treatment ever conducted. You think the results are very strong. There's no doubt in your mind—the method is working, and the kids you treat are getting better. There's only one hitch, a hitch that threatens to turn your dream into a nightmare: Your colleagues in the field don't believe your results. They think you're so committed to your scientific vision that you're overlooking the fact that the results may be due to a placebo effect. What's more, the Food and Drug Administration (FDA) is investigating the private foundation you've set up to remove your research from what you think is "too much scrutiny"—and a preliminary FDA report suggests that the agency thinks you're biasing your results by selecting the data.





Muscle-builder? Peter Law and his Cell Therapy Foundation have been under intense scrutiny lately, Law from his scientific peers, the foundation from the FDA.

This is the story of Peter K. Law, a charming, Chinese-born, Canadian-educated researcher whose proposed experimental cure for Duchenne's muscular dystrophy has his field in an uproar. Last month, at the first ever meeting of the Society for Cell Transplantation in Pittsburgh, Pennsylvania, Law presented his latest results on transplanting immature muscle cells into the leg muscles of boys with the disease. Law claims that 81% of his experimental patients experienced muscle strengthening or stabilization of their disease. "This is the first time that anybody has reported a successful experimental treatment for Duchenne's muscular dystrophy children using myoblast transfer therapy," Law said. "It is the ultimate gene therapy."

But not everyone agrees. While most of those in the field consider Law a pioneer in myoblast therapy, many feel he has gone too far, too fast, with too little reliable data to justify his aggressive treatment approach and his assertions of success. "I don't feel that the way Dr. Law has presented the results in his paper justifies the claim that he has shown significant muscle increase," says Jacques P. Tremblay of Laval University in Quebec, referring to Law's manuscript in *Cell Transplantation*, the society's new peer-reviewed journal.* Tremblay runs one of the handful of labs worldwide that have injected the immature muscle cells, called myoblasts, into Duchenne's boys.

With most of the world's experts gathered at the Pittsburgh conference, it became clear that Law's spectacular apparent success conflicts with a muddier picture emerging from other labs doing similar work. "The data coming out of the human studies is quite hard to interpret," said Terence A. Partridge, a myoblast pioneer from Charing Cross & Westminster Medical School in London. "Most experiments [by Law and others] have some confounding factor in them which makes you doubtful" of the results. Arguments about these "confounding factors" became so heated at the meeting that conference moderators cut off the discussion at least three times to keep the comments from turning nasty.

The end of the Pittsburgh conference hardly brought the debate over Law's work to a close. Indeed, over the past 2 years, since Law left the University of Tennessee at Memphis to form his own foundation, the controversy has been building to a fever pitch. The dispute has become so intense, in fact, that it threatens to obscure the potential value of the revolutionary cellular treatment, which many experts consider promising. Sometimes such scientific slugfests are heightened by the fact that the research is arcane. But in this case the scientific issues are straightforward, even if the interpretation of the facts varies wildly, depending on whether Peter Law or his critics are consulted.

Boys born with Duchenne's muscular dystrophy inherit a defective gene on the X chromosome. The mutation makes them unable to produce a protein called dystrophin, and that lack is catastrophic for the muscles. Muscle fibers lacking dystrophin go through cycles of deterioration and regeneration until the repair capacity is exhausted and the muscle dies. By age 10, muscle weakness drives most Duchenne's boys into wheelchairs; by age 20, they die of heart or respiratory failure. The disease strikes 1 in every 2500 male births, and as many as 30,000 boys are born in the United States with the illness each year, according to the Muscular Dystrophy Association (MDA).

The experimental treatment at the heart of the controversy, myoblast transfer therapy, is something like organ transplantation. Instead of transplanting a heart or liver, however, the physician injects single cells, each carrying a normal dystrophin gene. Myoblasts normally repair muscle fibers by fusing with the fibers, and the transplanted cells can join with a defective Duchenne's muscle fiber and cure it. Animal experiments, including many by Law, show that myoblasts from healthy rodents injected into mice that suffer from an illness similar to muscular dystrophy will fuse to the defective muscles and make dystrophin. Law's research suggested that the animals get stronger after treatment.

These findings, and the others that Law has made, can't be easily dismissed. At 46, he is the holder of a Ph.D. in neurophysiology from the University of Toronto and has conducted animal research on muscular dystrophy for more than 15 years, first at Vanderbilt University in Nashville, Tennessee, then at the University of Tennessee, where he be-

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came a full professor. Until the recent hubbub, his work had regularly received high marks from his peers, including study sections at the National Institutes of Health, which funded his animal research. A current grant from the National Institute of Neurological Disorders and Stroke runs until March 1993, and officials there said they saw no reason to be concerned about Law's work.

But most of that record concerns the less controversial arena of animal research. In the late 1980s, the animal results convinced Law that myoblast transfer was ready to move into human studies. After getting the necessary permissions from review committees at the University of Tennessee, Law, with pediatric neurologist Gerald S. Golden, injected myoblasts into the muscle that controls the big toe on one foot; the other foot, serving as a control, received a sham injection. The children also received the drug cyclosporin to prevent rejection of the foreign cells.

For the first Duchenne's boy, the researchers knew which foot received the myoblast injection and which the placebo. For the remaining 10 subjects, the study was double-blinded, with pediatrician Golden keeping the code book that recorded which leg had received the myoblasts and which the placebo. The Tennessee team watched while the treated toe muscle in the first child appeared to get stronger. They then broke the code on the next two children, who had also seemed to improve. Based on those three patients, only two treated in a double-blinded fashion, Law declared the therapy a success. But the data from the remaining eight patients were never analyzed.

Law explains the failure to analyze the remaining patients by saying he no longer had the code book after he quit the University of Tennessee in 1989 and started his foundation, where he intended to carry out a more ambitious human trial. He quit Tennessee, he says, because it took too long for his experiments to be cleared by the university's institutional review boards (IRBs)—and he feared the "excessive review" would unduly delay his next set of human studies. A university spokesman acknowledged that Law underwent several reviews before conducting his first study but said Law "didn't have more reviews than anyone else."

In any case, Law created his own Cell Therapy Research Foundation in Memphis, and while the patients from the first experiment moved with him to the foundation, Golden remained at the university with the code books. Despite attempts to get everyone together, an analysis of the remaining patients was never carried out. No one yet knows whether the muscle in the big toe improved for the remaining eight children. Law acknowledged that "the last eight were not analyzed because we don't have the code book" but dismissed them, saying that the second study "is the one that is important."

Undaunted by the limitations of the first study, Law launched his second clinical trial in May 1991. To date, he has treated the major leg muscles of 32 boys, ages 6 to 14. In the treatment, doctors remove an eraser-sized plug of muscle from the boy's father or healthy brother and grow the cells in the laboratory until there are some 5 billion myoblasts. With the boys under general anesthesia for about 10 minutes, physicians use 48 injections to place the myoblasts into 22 muscle groups. All of the children received immune suppression with cyclosporin for 6 months to prevent rejection of the myoblasts.

All of the muscles in all of the boys received treatment; no muscles were used as a control group. To measure the effectiveness of the therapy, Law's team used a specialized machine to measure muscle strength in each boy's legs 3 months before treatment, immediately before treatment, and 3 months after treatment. At the Pittsburgh meeting, Law reported that muscle strength improved in 43% of the treated muscles by an average of 41% when compared to muscle strength before treatment. In addition, 38% of the muscles stopped deteriorating after treatment, and only 19% completely failed to respond.

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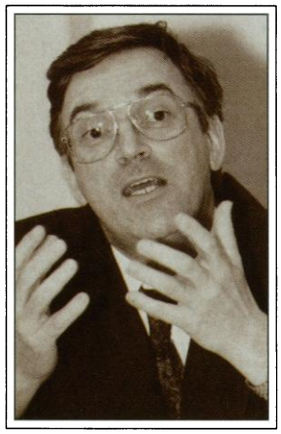
–Jacques Tremblay



If these results are correct, Law has scored a significant improvement in treating Duchenne's muscular dystrophy. But other scientists believe his results are flawed because he did no control experiments for the effects of immune suppression—an omission all the more striking because immune suppression temporarily has been shown in many studies to strengthen (temporarily) muscles affected by the disease. "I am astonished that you haven't controlled for cyclosporin," Robert H. Brown Jr. of the Massachusetts General Hospital in Boston said to Law during one meeting session.

Law acknowledged that using a control group would be standard scientific practice. But it is a practice that, in this case, he rejects as unethical. "It is not possible for us ethically [to use a placebo treatment] because we already know from our phase one study that the sham-injected muscle showed a decrease in function," he said. Law believes that sham injections of saline into muscles affected by the disease damage them, and that they deteriorate faster. Several scientists interviewed by *Science*, however, said that because Law treated only two patients in a double-blind fashion in the first study, those results could not justify dropping controls.

Law also rejects the notion that cyclosporin causes muscles to strengthen. He did not see that effect in his first study, he says. In addition, he claims that in his second study the children's untreated upper body muscles continued to deteriorate even though they received cyclosporin. In an interview he cited a recent mouse study that he said failed to show any effect of immune suppression on muscle strength.

The possibility that Law had ignored a potential placebo effect wasn't the only criticism by scientists at the Pittsburgh conference, however. Some also questioned his use of muscle strength as the best way to evaluate the treatment's effectiveness. Several said that the real test is not muscle strength—which can be confused by other factors—but whether the treatment corrects the lack of dystrophin protein. "There have been 10 to 15 years of controversy of using [muscle strength to show improvement]," said Donald S. Wood, the MDA's director of science and technology. "Giving kids anything, and telling them they are going to be better, makes them transiently better." Tremblay says that researchers can never be certain they are measuring a child's maximum exertion. Strength measurements can also be misleading, several experts said, because they are affected by growth: As the patient's muscles deteriorate, he is also growing, and that can make the muscle appear to be getting stronger.

But Law staunchly defends his use of muscle strength as a criterion, saying that the measurements are not confounded by other effects. "We have a perfect control," he said, "strength before and after transfer on the same muscle."

Law dismisses much of the criticism as professional jealousy. "Obviously, they do accept the concept [of myoblast therapy]. Perhaps the major reason [for the criticism] comes from the fact that we get positive results and they don't." He said the other teams have obtained poorer results because they made technical mistakes, including injecting too few myoblasts, using many muscle-damaging injections, and treating few muscles.

While Law struggles to fend off criticisms of his science from colleagues, he must also contend with questions about his Cell Therapy Research Foundation and its practices. While patients are not charged for his experimental therapies, the families are asked to help raise money—a practice that is unusual among foundations. And because Law is outside the university system, he is not required to have the institutional review board (IRBs) that universities must have. Instead, he set up two "independent review boards" to approve his human experiments. Who are the members? Law refuses to say. "We decided not to talk about [the board membership] because the [members] are very worried that pressure will be put on them because [myoblast transfer therapy] is so much in the limelight," Law said.

Concerns about the foundation's activities caused families of children receiving treatment, and some physicians, to complain to the FDA. An FDA investigator inspected the Memphis foundation in May. A preliminary report from the FDA site visit, obtained by *Science*, included at least two allegations that experts think are potentially serious, if true: a selection of data that could introduce bias into the results and conducting experiments with more subjects than Law's own review board gave permission for.

After *Science* showed the FDA findings to Don Wood, MDA science director, Wood said: "It is obvious to me that [Law] is doing a lot of data selection. It calls into question all the conclusions he is making. If you had all the data, maybe the conclusions would be totally different. Maybe not. The problems [FDA found] suggest that we are not seeing the true picture on whether or not the kids are getting stronger from the treatment. This is serious."

Law strongly denied that he is biasing the results but acknowledged that some data are discarded. "When a child is undergoing manual testing of strength, sometimes a muscle cramp would develop. The muscle cannot generate as large a force because the patient is hurting. The result is registered on the [testing machine's] screen. If you take that data into consideration, knowing full well that the patient is having a muscle cramp, the data would not represent maximum force development. When that happens, we exclude that data." He added: "None of the FDA observations goes to the fundamental validity or reliability or the quality of our research." He rejected the FDA allegations as a failure of the FDA investigator to understand the foundation's research.

After reviewing Law's files, the FDA's investigator does conclude that Law's team may have treated more boys with myoblast therapy than had been approved by the two "independent review boards" that reviewed his work. This is a potentially serious infraction of ethical standards, said John C. Fletcher, head of biomedical ethics at the University of Virginia Medical Center, Charlottesville, Virginia; Fletcher was a pioneer in establishing IRBs at research universities in the 1970s. "The number of subjects is very important, particularly with more risky research. It is very common for an IRB to limit the number of subjects in difficult or controversial research to a small number at first, and then increase it. But you may not exceed the number that the IRB limits you to."

Law denies he exceeded his approved limits. Initially, he said, the independent review boards approved a Phase II trial with 30 children. At Pittsburgh he reported treating 32 subjects, but, he says, the additional patients had also been approved by the review boards. "There is an approval letter in the file for an additional five subjects."

Even if the Memphis scientist is able to show that he complied with the dictates of his independent review boards, ethicist Fletcher criticized those very boards. "If he wanted to have a good review, he could have gone to a university IRB and asked them to do it as a service," Fletcher said, adding that "some private organizations do this."

Law has hired a lawyer to formulate his response to the FDA's preliminary report. Government officials refuse to comment on the FDA investigation or when it will conclude. FDA will not say whether it plans any action against the Cell Therapy Research Foundation. The matter is complicated by the fact that the FDA itself is only now struggling to define its role in regulating cellular therapies. In the past, such biological treatments have not been regulated, and Law was not required to file the equivalent of an investigative new drug application to conduct his studies. In the future, however, that may change—particularly if the agency's review of Peter Law's controversial foundation takes on a higher profile.

–Larry Thompson

Larry Thompson is a science writer living in Bethesda, Maryland.

COLD FUSION

Where There's Heat There's Yen

TOKYO—Officials at Japan's Ministry of Trade and Industry (MITI) this week announced that they hope to launch a 5-year program next year to study the systems in which the University of Utah's Stanley Pons and his British colleague Martin Fleischmann claimed they saw evidence of cold fusion. Sheer folly, given that most of the world's physicists have written off cold fusion as impossible? Not so, says MITI—it's just Japanese pragmatism. All MITI is interested in is the continuing reports of excess heat generated in the hydrogen-palladium cells studied by Pons and Fleischmann and the possibility of putting any new phenomenon—even if chemical rather than nuclear in origin—to industrial use.

An official from MITI's National Resources and Energy Agency, who spoke on condition of anonymity, explained that MITI has no intention of joining the debate over whether "cold fusion" really occurs. "We are not concerned with that kind of effect and leave this argument to the academic field," the official said. "We are more interested just in the fact that something is happening that is producing heat, and this might have some practical applications." Improved fuel cells and new types of batteries are possibilities the official mentioned.

Despite their official indifference to the "academic" debate, MITI officials took advice from Pons and Fleischmann as they put the finishing touches on their program. Last week, MITI held a closed seminar on cold fusion in Sapporo, the regional capital of the northern island of Hokkaido. Pons and Fleischmann were present, along with researchers from Japanese universities and private companies as well as cold fusion researchers from other countries.

Barring last-minute objections by the Japanese Ministry of Finance, the new project will begin in April of next year with an initial budget of $1 million to $3 million. Scientists from universities and from about 10 leading Japanese utility, electronics, and metallurgical companies—many of which already have their own cold fusion programs—will participate in the program, according to Osaka University professor of engineering Akito Takashashi, Japan's leading cold fusion researcher (*Science*, 24 April. p. 438). Initial efforts in the new program will involve the collection of data from around the world and a series of small-scale research projects.

Whatever MITI's intentions, Takashashi is confident that the project will vindicate Pons and Fleischmann. In his own experiments he claims he is seeing both heat and neutrons. "I don't believe that this is a chemical reaction, but actual cold fusion," he says. But if he turns out to be right, the National Resources and Energy Agency may have to end its official disinterest in the cold fusion debate. The anonymous official there points out that his division has responsibility for energy sources such as fuel cells, solar power cells, or wind machines. Nuclear energy, he says, is not within his jurisdiction.

–Frederick S. Myers

Frederick S. Myers is a science writer based in Tokyo.