years into the future. Then they modified the data by adding or subtracting random errors of just the kind thought to plague real observations and ran the orrery again. The random errors had little effect on the predicted positions for Jupiter and Saturn, but they left the positions of Uranus and—even more so—Neptune distinctly smeared out. Indeed, the smearing looked remarkably like that expected from the gravitational pull of an unseen planet.

"This suggests to us that the discrepancies do not require a tenth planet," says Quinlan. That's not to say it can't exist, he quickly adds. But tracking it down wouldn't be easy. The finding that random errors can account for the apparent orbital anomalies of Uranus and Neptune means that the signature of a Planet X would be lost in the noise unless it were much more massive than Harrington predicts.

Theorist David Hughes of the University of Sheffield goes further, arguing that even if observational error weren't blurring the picture, there would be nothing to see. There hasn't been enough time yet in the history of the solar system for a planet to form at the distances proposed for Planet X, he argued at the RAS meeting. His calculations show that, given the scarcity of primordial material at those distances, it would take 10 billion years—twice the solar system's age—for anything substantial to condense. "If you believe this theory, then the solar system probably ends at Neptune [currently the farthest planet from the sun]," he says.

But even if Hughes is right, Harrington maintains, Planet X could slip through a loophole. Perhaps it formed closer to the sun, then was flung out toward the edge of the solar system by the chaotic dynamics that may have dominated the planetary motions. Indeed, Harrington and his USNO colleague Thomas van Flandern think that scenario could simultaneously explain the existence of Planet X, Pluto's small size, and some peculiarities of Neptune's satellite system. They propose that on its way out to the edge of the solar system, Planet X veered close to Neptune and stripped away one of its moons, which became the planet we now know as Pluto.

Harrington calculates that the mass Planet X would need to succeed in that celestial abduction is close to that needed to cure the orbital discrepancies of Uranus and Neptune. Far from pronouncing Planet X dead, Harrington says, he is light-heartedly rechristening it. The new name he has chosen: Panacea. ■ ROBERT MATTHEWS

Robert Matthews in an Oxford-based journalist who covers science for the Sunday Telegraph *in London.*

Putting New Muscle Into Gene Therapy

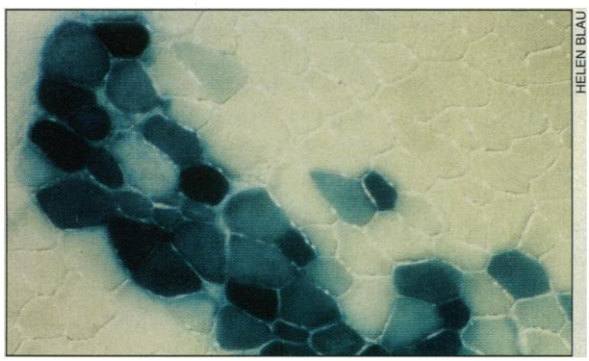
Immature muscle cells may provide an efficient system for delivering therapeutic new genes into the body

GENE THERAPY, THE INSERTION OF THERAPEUTIC genes into a recipient's cells, holds enormous promise for curing many diseases, both inherited and noninherited. But for that therapy to succeed, researchers must develop an efficient method for delivering active new genes into the patient's cells. And that's been harder than it sounds. In fact, most of the delivery systems tried so far have not worked out well. Now a new contender is trying to muscle in—and early results with lab animals look promising.

In work reported on pages 1507 and 1509, two research teams, one led by Helen Blau of the Stanford University School of Medicine, the other by Jeffrey Leiden and Eliav Barr of the Howard Hughes Medical Institute at the University of Michigan Medical Center in Ann Arbor, have demonstrated the feasibility of using immature muscle cells called myoblasts to carry genes into the muscle fibers of mice.

"A few years ago nobody would have dreamed that myoblasts could be a gene delivery vehicle."

—Gary Nabel



HELEN BLAU

Right at home. *Myoblasts, carrying a gene that makes them blue, become part of the recipient animal's muscle.*

One obvious potential application of the technique is to treat the genetic defects that cause muscular dystrophy. But the new method could have a much wider application as well, because the researchers have shown that the myoblasts, which were genetically engineered to contain the human growth factor gene, secrete the growth factor into the animal's blood. Engineered myoblasts might therefore be used not only to cure muscle cells but to deliver a wide variety of substances that either act in the blood or are transported by the blood to other tissues. A prominent possibility: insulin for treating diabetes.

The success with myoblasts caught many in the gene therapy business by surprise. "A few years ago nobody would have dreamed that myoblasts could be a gene delivery vehicle," says Gary Nabel of the Howard Hughes Medical Institute, who is exploring ways of using gene therapy to treat cardiovascular disease. For one thing, it seemed highly unlikely that myoblasts could be coaxed into secreting physiologically significant amounts of the desired protein into the bloodstream—a key need in gene therapy. "It had always been the dogma that [myoblasts] weren't secretory cells," says Leiden. But, as the current work shows, the dogma was wrong.

In showing the fallacy of that dogma the two groups used different "vectors," or vehicles, for carrying the human growth factor gene into mouse myoblasts in culture. Blau and her colleagues made use of a modified retrovirus; Leiden and Barr used a plasmid. That difference aside, the procedures and results were similar. Both groups injected the engineered myoblasts into mouse muscles and subsequently found physiologically significant levels of human growth hormone circulating in the serum of the mice, a finding that indicates that the implanted cells were manufacturing and secreting the protein. Best of all, both teams have seen hormone secretion sustained over a fairly long period—up to 3 months in the Blau lab.

That's a marked improvement over the results with previous gene delivery systems, which have used several cell types including

white blood cells, keratinocytes, fibroblasts, and liver cells. "Virtually no cell type used so far has delivered consistent high levels of gene product over a long period of time," says Blau. The others worked poorly for one of several reasons. Either the "on switch" of the therapeutic gene was inactivated, or the carrier cells were lost or destroyed in the host body, or the cells survived and produced protein, but became isolated from the blood supply, preventing the protein from getting into the blood.

Myoblasts do better than cells used in previous systems, both groups find, because they eventually differentiate and fuse to existing muscle tissue. "Because the cell is incorporated into an existing structure, it is not just tolerated, it is nurtured," says Blau. The result, she says, is that the implanted cells are likely to be longer lived than cells that have been injected into a foreign tissue. Theoretically, she adds, the implants could last the patient a lifetime.

In addition to these features, notes Leiden, the myoblast technique has some other qualities that could make it particularly useful for treating human patients. Myoblasts can easily be obtained by taking muscle tissue from an individual who needs gene therapy, and the genetically engineered cells can also be easily put back without causing damage to the patient's muscle.

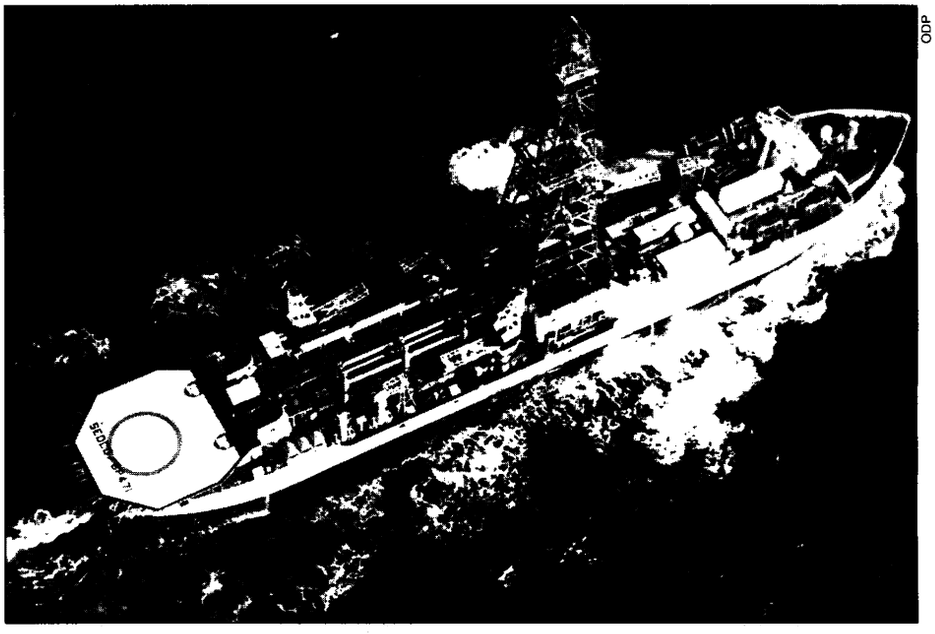
But amidst the general enthusiasm for myoblasts, some gene delivery specialists are sounding cautionary notes. First, both the Stanford and Michigan groups used established myoblast cell lines, which have been perpetuated in culture for many years. The results could be different with primary cells—those freshly removed from an individual. Drawing from his own experience with fibroblasts, Inder Verma, a specialist in gene therapy research at the Salk Institute in La Jolla, California, notes, "There is a question as to whether you can get sustained expression in primary cells." And he adds, cell lines are not acceptable for use in humans because, "they make tremendous amounts of protein, but they always make tumors."

Furthermore, although myoblasts have the "potential to export any protein product into blood serum, what looks good in animals may not look good in humans," says noted muscular dystrophy researcher Louis Kunkel of Harvard Medical School. Indeed, attempts to treat muscular dystrophy with injections of normal myoblasts have so far not worked very well. Preliminary data obtained in one trial, conducted by George Karpati's team at the Montreal Neurolog-ical Institute of McGill University, show that "not enough donor myoblasts fused with host cells to make a functional difference," says Karpati.

The myoblast fusion may have been poor because the cells may have difficulty penetrating the fibrous sheath of connective tissue that surrounds muscle fibers. Although previous work by Blau has shown that myoblasts can penetrate the connective tissue in mice, the number of myoblasts that can get across in humans "may be prohibitively low," says Karpati. Nevertheless, he notes that this may be more of a dilemma for replacing dystrophin, the protein lacking in muscular dystrophy, than for replacing secreted proteins. "You may not need so many myoblasts to take for a secreted protein like growth hormone," he says.

In spite of these difficulties, Leiden is very optimistic about the future of myoblasts for gene therapy. He envisions a day when scientists will be able to build a myoblast that can do whatever they want them to—maybe even sense blood glucose levels and secrete insulin as needed in response. "That's far fetched, but I'm not sure it's out of the question," he says.

Other researchers are looking even further ahead. Noting that removing a patient's cells and reimplanting them is cumbersome, Nabel suggests that in the future gene therapy may involve direct injection of DNA into muscle cells, a technique pioneered last year by Jon Wolff and colleagues at the University of Wisconsin, Madison, and Vical Inc. in San Diego, California, who injected marker genes into muscle cells. While direct injection of DNA has not yet produced high protein expression levels, Nabel is hopeful that the method can be improved. If so, the gene therapy of the future may indeed be a shot in the arm. ■ MICHELLE HOFFMAN



Still pursuing the deepest crust. *The 143-meter-long drill ship* JOIDES Resolution *may return to the deepest hole in the ocean floor for another try.*

Coming up Short in a Crustal Quest

Last month, deep-sea drillers at a site in the eastern tropical Pacific were licking their lips as their drill bit slowly churned down toward a long-sought goal of the international Ocean Drilling Program: the lower-most region of the layer-cake-like ocean crust. Based on reflections from seismic waves sent down ahead of the drilling, the researchers expected that the bottom layer of the cake—the solidified remains of the magma chamber that gave birth to the crust millions of years ago at a midocean ridge—was only meters away. But once again in their long quest, the drillers came away without their goodies.

Even though they had bored through the ocean crust to a depth of 2 kilometers—deeper than ocean drilling had ever gone before—researchers aboard the drill ship *JOIDES Resolution* encountered no sign of the rock, called gabbro, that is typical of sub-sea magma chambers. "Once again, we discovered you should take seismic interpretations with a grain of salt," says Bruce Malfait, the National Science Foundation's program director for the Ocean Drilling Program. "It's not clear from shipboard data what they drilled through," he continues, "but it's definitely not" the top of the gabbro layer.