New vectors for gene therapy aim to mimic viral vectors' pros without their dangerous cons

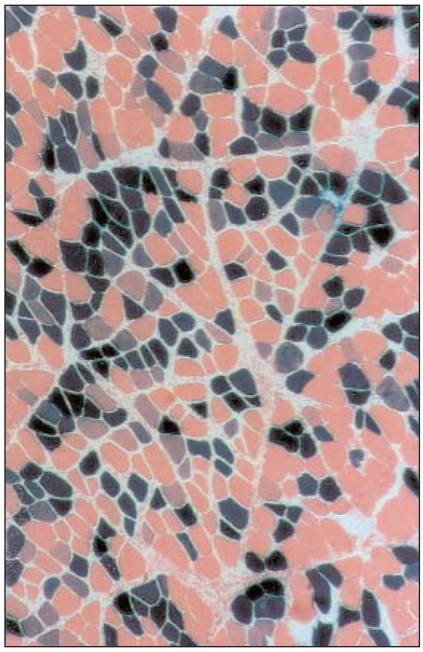
Gene Therapy: Safer and Virus-Free?

If fields of science go through life stages, then childhood ended abruptly for gene therapy on 17 September 1999, when a teenage volunteer named Jesse Gelsinger died in a gene therapy clinical trial at the University of Pennsylvania in Philadelphia. Sunny talks describing future therapies for genetic diseases were replaced by public scrutiny, congressional hearings, and new rules. Gelsinger's death was blamed on an out-of-control immune response to the virus physicians had used to ferry the useful gene into tissue, and it prompted a hard look at the safety record of so-called viral vectors. It also spurred renewed interest in nonviral methods to deliver genes, methods that have been quietly gathering steam for more than a decade.

Today, no gene therapy using any type of vector has been approved for clinical use. But researchers are working doggedly to develop methods that will deliver useful genes safely, to the right spot, and turn them on and off at will. Originally envisioned as treatments for hereditary diseases, gene therapies are now being developed to prevent and treat infectious diseases, cancer, heart disease, and other ailments. All of them rely on a gene's ability to produce a key protein when and where it's needed.

Viruses such as adenovirus and retrovirus are still the most popular vectors in lab studies and clinical trials. Viruses are well suited to gene delivery: They've evolved to home in on specific tissues, invade cells, and manipulate the cell's machinery to make viral proteins. But often they can be injected into a person only once or twice before the immune response they provoke poses a safety threat, as in Gelsinger's case. That response can also destroy the viral vector or the cells it infects, blocking production of the useful protein.

A spate of recent work has suggested that genes can be delivered effectively without using viruses. Most nonviral vectors fly under the radar of the immune system, and they're cheaper and easier to manufacture than viral vectors. But most of them have not been as efficient as viruses in shuttling genes into cells, and the genes that were delivered didn't remain active for long. That has begun to change in the past few years.



Muscular gene delivery. When naked DNA is injected into an artery that feeds the leg muscle of rhesus monkeys, up to 30% of the muscle fibers (blue) take up and activate the foreign gene.

In the race to develop a reliable gene-delivery method, researchers are putting money on a wide array of vectors, and so far no single method has taken the lead. Gene therapist Malcolm Brenner of Baylor College of Medicine in Houston, who is president of the American Society of Gene Therapy (ASGT), suspects that both viral and nonviral gene-transfer methods will be needed, depending on the disease being treated. "Nobody has the perfect vector," he says. "What we're looking for is horses for courses."

DNA, naked and otherwise

Back in 1989, when human gene therapy was still a dream, dogma had it that viruses were the best and perhaps only way to ferry therapeutic genes into animal tissue. But Jon Wolff, a gene therapist at the University of Wisconsin, Madison, suspected otherwise. Philip Felgner, then at Vical, a San Diego biotechnology company, had just devised a way to shuttle genes into lab-grown animal cells by coating them with positively charged lipids—basically, shrink-wrapping the DNA. The charge helps the construct, called a lipoplex, stick to cell membranes and pop genes inside the cell. Wolff tested the method in animals, injecting mice with RNA lipoplexes and then checking their tissue for the presence of an enzyme encoded by the RNA. To his surprise, mice injected with lipid-coated RNA failed to activate the gene. But the control mice, which had been injected with uncoated, or "naked," RNA, did crank out the enzyme. "I thought my technician screwed up and reversed the two samples," Wolff recalls. "But he repeated it, and it kept getting better and better."

Wolff was equally surprised a few months later, when genes ferried into muscle cells by loops of DNA called plasmids were expressed for weeks at a time. Researchers had thought that the only way to get long-lasting gene expression in animal tissue was to use a virus whose DNA stitched itself into the chromosomes of the recipient cells. But somehow, the naked plasmid DNA stuck around inside muscle cells, and the genes turned on and stayed on. "Even now I'm amazed," Wolff says. Naked DNA injections are still the simplest nonviral gene delivery method and so far one of the most successful.

Following Wolff and Felgner's early report, researchers quickly applied the naked DNA approach to a practical problem: building better vaccines. The method entails injecting a plasmid that encodes a protein from the unwanted microbe; the protein then provokes an immune response that would stop an infection. So far, clinical tests have been promising. For example, Stephen Hoffman, then of the Naval Medical Research Institute in Bethesda, Maryland, and his colleagues reported in 1998 that injections of plasmid DNA encoding a protein from a malaria parasite provoke a strong immune response in humans (*Science*, 16 October 1998, p. 476). And earlier this year, Harriet Robinson of Emory Uni-

CREDIT: J. WOLFF

Repair Kits for Faulty Genes

A balky appliance forces a choice: repair or replace. Defective genes impose the same choice. Most gene therapists have gone the replacement route, providing intact genes to make up for the defective version nature provided. But a few researchers are developing molecular toolkits to correct mutations in the genome. These so-called molecular targeting approaches don't touch the stretches of DNA flanking the faulty gene that help regulate its expression, so after the gene is repaired, the cell can still properly control when and how much protein the gene produces. That differs from gene replacement approaches, which don't necessarily replace all the normal expression signals. This strategy could make the difference in treating diseases that require the right amount of therapeutic protein at the right time. So far, gene-repair methods have corrected mutations involving the insertion, deletion, or substitution of only a handful of nucleotides at a time, and only a few of the methods have been tested in animals. But the following techniques offer potential means to achieve a longtime dream of gene therapists: a lasting cure for genetic disease.

Triplex-forming oligonucleotides (TFOs). These snippets of single-stranded DNA recognize double strands of DNA with identical or nearly identical sequences and nestle themselves into the double helix there to form a triple helix, or triplex. There are two versions of the method, one of which corrects mutations and the other of which purposely introduces mutations that stop production of a dangerous protein. To correct mutations, the TFO is linked to another snippet of DNA, this one double-stranded, that has the correct sequence of the defective gene. The double-stranded fragment shuffles itself into the genome near where the TFO has bound, replacing the misspelled portion of the gene.

To stop production of a protein, a single-stranded TFO is used alone, without a linked fragment of DNA. It snuggles into the misspelled portion of the gene, forming a triplex. The cell's repair enzymes are attracted to the triplex but don't know how to fix it. Instead they make new mistakes, introducing random mutations into the target gene. One drawback: TFOs work only on the minority of genes that have DNA sequences capable of forming triple helices.

Small fragment homologous replacement. This method takes advantage of the cell's ability to shuffle different copies of a gene by exchanging stretches of DNA between chromosomes, a process called homologous recombination. It uses a 400- to 800-base DNA fragment that's identical to part of the defective gene, except for the stretch that's to be repaired. The cell exchanges the fragment into one or both chromosomes. In the August issue of *Gene Therapy*, Dieter Gruenert's team at the University of Vermont in Burlington reported fixing a mutation that hampers breathing in mice with cystic fibrosis.

Viral gene targeting. Gene therapists usually use adeno-associated virus to deliver intact genes to replace defective copies. But apparently the virus can also be used to repair defective genes in the chromosome. Part of a normal gene is stitched into the single-stranded viral DNA, and the cell's repair machinery uses it to correct the mistake in its own genome. So far, the technique has repaired a variety of mutations in cultured human cells, including nucleotide deletions, insertions, and substitutions.

Chimeraplasty. Sickle cell anemia and many other genetic diseases are caused by misspellings of a single nucleotide in a single gene. In this approach, researchers create dumbbell-shaped hybrid molecules, part DNA and part RNA, that contain the correct spelling of the gene; the molecules seem to bind to the misspelled portion of the genomic DNA and fix the mistake. But this technique has met with hard questions since it was introduced in the mid-1990s. "It's fair to say there's been some controversy with regard to reproducibility," says molecular biologist Peter Glazer of Yale University School of Medicine. A handful of researchers defend the method, but few are pursuing it. **–D.F.**

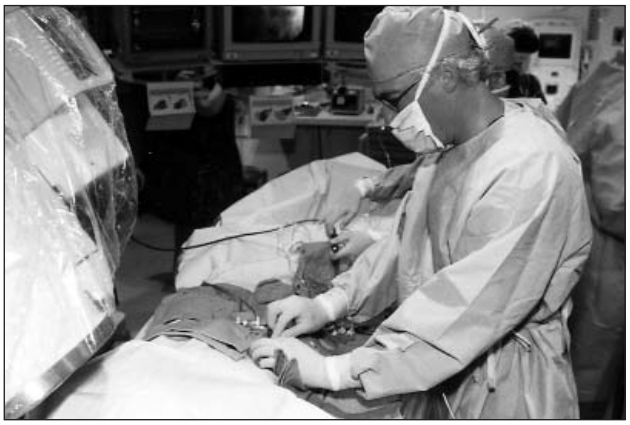
versity in Atlanta and colleagues reported that a naked DNA vaccine helps confer immunity in a monkey model of AIDS (*Science*, 6 April, p. 69).

Naked DNA therapies are also being tested against heart disease, cancer, and other disorders. The late cardiologist Jeffrey Isner of Tufts University School of Medicine in Boston and his colleagues developed a gene therapy for patients with coronary artery disease. The team injects a gene called *VEGF*, which boosts blood vessel growth, directly into patients' heart muscles by threading a special catheter through the arteries much as a surgeon would during angioplasty. The treatment gave promising results in a small phase I trial: New arteries sprouted from existing arteries, detouring blood around blockages to supply the heart muscle, according to work presented last week at the annual meeting of the American Heart Association. The technique, which is owned by a company Isner founded, called Vascular Genetics Inc. in Durham, North Carolina, apparently eases the severe pain of heart disease and improves patients' ability to exercise on a treadmill. The treatment could one day offer an alternative to bypass surgery, Isner told *Science* shortly before his death on 31 October (see p. 1670), and a similar method could help save the legs of diabetes patients and others whose circulatory disease is so severe they are candidates for amputation.

But naked DNA injections haven't worked well to deliver genes to tissues other than liver and muscle. To sneak genes into other tissues, researchers have tried coating the DNA with different combinations of lipids and polymers, which have been shown by trial and error to help cultured cells take up DNA.

Some such therapies are now being tested in the clinic. For example, Vical researchers have developed a lipid-coated plasmid that is injected directly into tumors to deliver the *HLA-B7* gene; this gene encodes a protein that sparks an immune response against the tumor. In a phase II trial, the immune response shrank tumors and prolonged life in eight of 73 patients with aggressive melanoma who had failed to respond to other treatments, company collaborators reported in May at the annual meeting of the American Society of Clinical Oncology.

A different gene-delivery strategy for head and neck cancer—composed of a gene called interleukin-2 coated with



CREDIT: ST. ELIZABETH'S MEDICAL CENTER

Straight to the heart. The late Jeffrey Isner injects naked DNA to treat a patient with coronary artery disease.

Viral Vectors Still Pack Surprises

Viruses may be lowly parasites, but their power to invade cells has won them a big part in gene therapy. Stripped of disease-causing elements, they work as natural syringes to inject DNA into human cells. Such "viral vectors" now dominate gene therapy: Nearly three-quarters of all protocols use them. Even so, researchers view their parasitic past with suspicion and worry about unforeseen problems in the clinic. The tamest viruses have produced surprises, as researchers using adeno-associated virus (AAV) learned recently.

In September, federal overseers asked Stanford University's Mark Kay to put "on hold" a clinical trial using an AAV vector to treat hemophilia B, an inherited blood disorder. The reason: Signs of AAV in the patient's semen raised a concern that gene therapy might have changed the man's inheritable DNA.

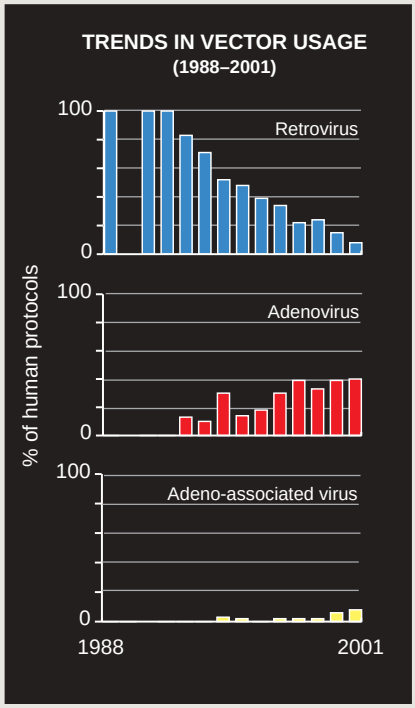
It's not unusual to detect traces of a vector after gene therapy, Kay says. But in this case, the signal persisted "at a low level" for weeks before it cleared, he says. Kay alerted the Recombinant DNA Advisory Committee (RAC), an oversight group at the National Institutes of Health (NIH), and the Food and Drug Administration (FDA). The FDA asked for a pause; the case will be discussed in the RAC on 5 December.

The RAC forbids any gene therapy that changes the "germ line"—eggs or sperm—either inadvertently or for genetic enhancement, because germ line mutations could be passed on to future generations. Kay already takes steps to prevent inadvertent alterations. His team informs patients that there is a small risk of germ line changes and, before therapy, offers to bank the sperm of male patients and asks them to use barrier contraception until their semen is clear of vector signal.

Kay doubts that germ line changes occurred in this hemophilia patient. Instead, he thinks the AAV signal probably came from typical "shedding" of vector seen in body fluids. But he hopes the RAC discussion will lead to a consensus on risk. "We're changing germ lines all the time in cancer therapy" with DNA-mutating chemotherapy—and that doesn't bother people, Kay notes. But he understands that gene therapy is "new territory." He favors guidelines that would allow these safety trials to continue if the probability of germ line alteration remains low.

Widely regarded as ultrasafe, AAV ran into another hurdle earlier this year. Although wild-type AAV infects many people, it doesn't seem to cause illness. But researchers got a scare last winter when mice that had been injected with an AAV vector developed liver tumors. This discovery prompted a short pause in two clinical trials using an AAV vector and an inquiry by U.S. health agencies in March. A joint review by FDA and RAC concluded that the AAV vector probably did not cause the mouse cancers. Clinical trials using AAV have resumed.

The cancer scare arose when molecular biologist Mark Sands of Washington University in St. Louis, Missouri, was reviewing data on mice in a gene therapy test. Sands is developing an AAV vector to treat people with inherited enzyme deficiencies, concentrating on a fatal disorder called mucopolysaccharidosis type VII, in which the body fails to process waste in lysosomes. Sands created knockout mice with this disorder and successfully treated them with AAV-vector gene therapy. But during a routine pathology review last year, he discovered that three of five mice sacrificed late in life—at 18 months, the human equivalent of 55-year-olds—had massive liver or blood vessel tumors. "It scared me. I had never seen tumors like this," says Sands, although he had used identical mice in many experiments—and this particular group of 59 had seemed tumor-free until the end of the study. On reexamination, three additional animals, the youngest sacrificed at 8 months, were found to have had tumors.



Shifting focus. This sample illustrates the relative decline of retrovirus vectors (active only in dividing cells) and the rise of adenovirus and adeno-associated virus vectors (active in dividing and nondividing cells).

Sands was concerned that the AAV vector might have inserted new genes into the mouse DNA in a way that triggered cancerous growth. After reviewing the data, experts at a joint FDA-RAC meeting in March ruled out "insertional mutagenesis" as a cause of cancer. Sands agrees. But that does not rule out other possible vector-induced changes, Sands notes.

What actually caused the cancers remains unclear. Some panel members suggested that the knockout mice may have been prone to liver cancer. R. Jude Samulski of the University of North Carolina, Chapel Hill, a vector expert who took part in the RAC review, suggests that when these mice are cured of their inherited enzyme disorder, another genetic flaw may cause cancer in old age. But Sands hasn't seen evidence that the mice are prone to cancer. And it troubles him that other researchers have not allowed mice to live as long as he did for safety testing.

Although the scientific puzzle remains unsolved, Mark Kay and Terence Flotte, a gene therapist at the University of Florida, Gainesville, are confident that AAV vector can be used safely in gene therapy. The NIH and FDA, meanwhile, have asked Sands to do another mouse study to see if he can repeat the results. The research will require "hundreds" of animals, he says, and "years" to complete.

–ELIOT MARSHALL

cholesterol and a synthetic lipid—also gave promising results in a phase II trial in patients with tumors that could not be surgically removed, a team from Valentis Inc. of Burlingame, California, reported at the ASGT annual meeting in June. The treatment kept cancer from spreading for more than 4 months when combined with traditional chemotherapy—38% longer than patients receiving chemotherapy alone.

Up-and-coming vectors

The number of clinical trials using nonviral vectors for gene therapy is growing (see table on p. 641), but many diseases can't be treated using the nonviral gene delivery methods that are farthest along. That's because most methods have delivered only low levels of active genes for short periods of time. Researchers are currently hammering out other approaches in the lab. They're trying to improve upon current vectors by finding ways to penetrate a higher percentage of cells in target tissues and make imported genes last longer once inside the cells.

Short-lived gene expression is fine for vaccines, cancer therapies, and angiogenesis. Indeed, Isner called it "a major-league safety advantage" for vascular gene therapy, because only temporary gene expression is needed to grow new vessels, and because in-

SOURCE: NIH

sertion into the genome—the goal of some viral-based gene therapies—could disrupt other genes, possibly causing cancer. But to treat other diseases, therapeutic genes might have to pump out more protein for longer periods. Today's viral vectors still do this better than nonviral ones do, but lab experiments with new nonviral methods are closing the gap.

For example, a method called electroporation, developed by immunologist Richard Heller's team at the University of South Florida in Tampa, transfers genes more than 80 times as efficiently as naked DNA injections. The team injects DNA into the target tissue—usually skin, muscle, or tumors—and uses a specially designed electrode to apply an electric field, which punches temporary holes in cell membranes that allow DNA into the cell. The method hasn't been tested in the clinic, but it's close: Gene therapist Lou Smith of Valentis and his colleagues recently used electroporation to transfer a blood-clotting gene to hemophiliac dogs, temporarily eliminating symptoms of the disease, according to work presented at a meeting in May sponsored by the National Hemophilia Foundation. And Heller's team reported at the June ASGT meeting that the method helped deliver a cancer-fighting gene called interleukin-12 into skin tumors, causing some of them to disappear in mice. They're now testing the method to see if it can provoke an immune response powerful enough to clear tumors in animals with melanoma.

Another novel nonviral strategy, developed by geneticist Richard Selden's team at Transkaryotic Therapies in Cambridge, Massachusetts, also improves gene-transfer efficiency. Instead of ferrying genes into cells inside the body, the researchers remove cells, insert genes, grow lots of modified cells in the laboratory, and then inject the cells into the abdominal cavity. The researchers used the method to transfer a gene encoding a blood-clotting protein called factor VIII into skin cells taken from six hemophiliacs, they reported in the 7 June issue of *The New England Journal of Medicine*. When the cells were returned to the body, they produced the clotting protein. Four of the six patients needed less of their usual injected form of clotting protein and exhibited less bleeding for up to 10 months after the injection.

Long-lived gene expression has proved elusive for most nonviral vectors, in part because none of them stitch the useful gene into the genome of the host cell. But Mark Kay's team at Stanford has recently devised the first nonviral vector that has this power. Two plasmids are simultaneously injected into the tail vein of a mouse. One plasmid includes a therapeutic gene connected to pieces of a transposon, or jumping gene. The second plasmid encodes an enzyme that helps the hybrid gene on the first plasmid jump into the chromosome. When both plasmids were simultaneously injected, they sewed a key blood-clotting gene into liver cells of hemophiliac mice, where it pumped out enough protein to allow blood to clot normally, the team reported in the May 2000 issue of *Nature Genetics*.

Kay's team also happened on a new way to achieve long-lived expression by delivering linear DNA fragments that don't insert themselves into the genome. These fragments persist in mouse liver cells for at least a year—about half the lifetime of a mouse, the team reported in the March issue of *Molecular Therapy*. "The persistence issue is being solved," Kay says.

To get these long-lived plasmids into the liver, Kay used a method called hydrodynamics, developed by Wolff's team and Dexi Liu's team at the University of Pittsburgh. The method involves quickly injecting the tail vein of a mouse with naked DNA in a huge volume of saline, roughly the entire blood volume of the animal. The pressure somehow forces DNA out of blood vessels in the liver, where many of the liver cells take up and express the foreign genes.

No one proposes injecting people with a proportional amount—nearly 5 liters—of DNA-containing saline. But hydrostatic pressure could still help deliver genes to human tissue. For example, Wolff's team injected DNA into arteries that feed the arm and leg muscles of rhesus monkeys, using a blood-pressure cuff to temporarily increase blood pressure. As they reported in March in *Human Gene Therapy*, the method delivers a reporter gene to about 30% of the muscle cells—a level of efficiency that rivals that of viral vectors. Wolff's team and colleagues at a company he founded, Mirus Corp. (a subsidiary of PanVera Corp. of Madison, Wisconsin), and at Transgene of Strasbourg, France, are planning a small clinical trial next year to see whether the pressure-cuff method can replace a defective muscle gene in young adults with Duchenne muscular dystrophy.

Surgically clamping blood vessels does the gene-delivery trick, too, and can reach muscles that are inaccessible to a pressure cuff. In the July issue of *Molecular Therapy*, Leaf Huang's team at the University of Pittsburgh reported inserting a key gene to repair the diaphragm muscle of mice with muscular dystrophy (MD)—a crucial target because many MD patients die of suffocation when their diaphragm muscles fail to pull air into the lungs. The researchers surgically clamped the outgoing blood vessel for a few seconds, raising the blood pressure enough to deliver the therapeutic gene; Huang suspects that similar clamping methods could help push therapeutic genes into other organs as well.

GENE THERAPY CLINICAL TRIALS WORLDWIDE

Vector	Open Trials	Examples of diseases
Viral		
Retrovirus	157	Many cancers, AIDS, severe combined immunodeficiency, rheumatoid arthritis, graft-versus-host disease, multiple sclerosis, osteodysplasia, hemophilia
Adenovirus	132	Many cancers, peripheral artery disease, cystic fibrosis, Canavan disease
Pox virus	35	Many cancers
Adeno-associated virus	7	Prostate cancer, cystic fibrosis, hemophilia B
Nonviral		
Lipofection*	57	Many cancers, cystic fibrosis, coronary artery disease, restenosis
Naked DNA	47	Many cancers, peripheral artery disease, coronary artery disease, peripheral neuropathy, open bone fractures
RNA transfer	5	Many cancers
Gene gun†	4	Melanoma, sarcoma

* Includes liposomes and various packages of lipid, polymer, and other molecules.
† DNA coated on small gold particles and shot with a special gun into target tissue.

SOURCE: THE JOURNAL OF GENE MEDICINE

Whether or not it can be adapted to the clinic, hydrodynamics proves that high-efficiency gene transfer is possible without viruses, Kay says. It's also the first method to rapidly pinpoint the best candidate genes for gene therapy. Researchers create small pools containing different genes, inject each pool into mice, and see quickly which contains a gene that helps treat the disease. With their candidates thus narrowed down, researchers can inject mice with each gene in the pool to identify which one helped. That's much quicker than cloning each candidate gene into a viral vector, and it could be important for diseases such as cancer, in which no one's sure which genes will prove effective. Liu says that the discovery of new therapeutic genes, together with more efficient delivery, "will make the field jump."

Vectors tailored to tissues

When viral gene therapy vectors are injected into the bloodstream, the viruses protect their gene payload, home in on their target tissue, and deliver the genetic goods—as viruses have been doing for eons. Some researchers are devising complex nonviral vectors that act more like viruses, using tools developed by a generation of drug-delivery specialists. The long-term goal is to transfer genes to the correct tissue to produce the desired clinical effect, says drug-delivery specialist Sung Wan Kim of the University of Utah in Salt Lake City.

Custom-designing vectors, Kim says, relies on several strategic decisions: whether to inject into the bloodstream or directly into the tissue; which combination of polymer, lipid, and other molecules to use for a particular tissue; and whether to attach another molecule to help target the complex to the correct cells. Despite the complexity, it's beginning to work: In the August issue of *Gene Therapy*, Kim's team reported a three-part system called TerplexDNA that delivers genes to rabbit heart tissue 20 to 100 times more efficiently than naked DNA. The vector includes DNA, a positively charged polymer to help protect DNA from enzymes that would chop it up, and a lipid that heart muscle cells recognize and take up.

The team has also developed a way to deliver useful genes by injection into the bloodstream. The method uses DNA wrapped in a soluble, degradable polymer to target white blood cells. In the July issue of *Gene Therapy*, the team reported that one injection in mice helped deliver two genes to white blood cells throughout the body. They pumped out proteins that made their way to the pancreas and blocked the autoimmune reaction believed to cause juvenile diabetes.

Gene therapist Leonard Seymour's team at the University of Birmingham, U.K., has developed another way to ferry genes through the bloodstream to target tissue: cloaking the genes in a two-part polymer shell and freeing them where they're needed. A polymer called polylysine packs the DNA into small particles, and a second polymer makes it slippery and able to evade immune proteins and cells. Once inside the target cell, the chemical environment causes the polylysine to break apart, liberating the DNA for expression. "It works amazingly well," Seymour says. Eventually, the team would like to add guidance molecules—such as a specific antibody, peptide, or sugar—that are recognized and taken up only by particular tissues, making targeted delivery possible.

Complex nonviral carriers are a long way from the clinic, but they may offer a glimpse of future gene therapies. Years from now, gene therapy vectors might be a sort of semisynthetic virus, combining the best of today's viral and nonviral carriers, ASGT president Brenner predicts. Such a vector would make precise and permanent fixes to genetic defects that underlie disease by homing in on a specific tissue and replacing or fixing a defective gene, while safely avoiding the potential dangers of viral vectors. But other experts see a different future, in which genes are given temporarily and produce a precise dose of protein for just as long as it's needed. In short, says Felgner, "the idea would be to inject genes like any other drug." **–DAN FERBER**

AN INTERVIEW WITH JOHN MARBURGER

Terrorism, Money, Contacts Top Science Adviser's Agenda

Long-awaited appointee arrives amidst new war on terrorism and ongoing battles over science funding and priorities

John Marburger's job is to advise the president on science. But he isn't expecting extensive face time with George W. Bush. Rather, his experiences as a university president and director of a national laboratory have taught him the importance of chain of command. "I would regard having to talk with the president as an indication [that] something is very seriously wrong somewhere," says the 63-year-old physicist, who on 23 October became director of the Office of Science and Technology Policy (OSTP) as well as assistant to the president for science and technology.

Marburger steps into a job very different from what he expected when he was nominated in June. The events of 11 September have put terrorism at the top of his agenda, he says, adding duties as science adviser to the new White House Office of Homeland Security. In his first few weeks on the job, he has been busy meeting with groups and individuals inside and outside the government, and he has been "deeply involved" in preparing the 2003 budget request, which will be sent to Congress in January.

Marburger is the 14th scientist to hold the White House post, created by President Dwight Eisenhower in 1958 to give top politicians easy access to technical advice. After earning a doctorate in applied physics from Stanford University in 1967, Marburger taught and conducted research at several universities. He spent 14 years as president of the State University of New York, Stony Brook, before taking over an embattled Brookhaven National Laboratory in 1997. He is credited with improving the Upton, New York, lab's relationship with its neighbors, who had forced the shutdown of an aging research re-

CREDIT: MARTY KATZ

Reaching out. One of John Marburger's (left) first tasks has been to forge links with science community stalwarts, such as House Science Committee chair Sherwood Boehlert (R–NY).