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-

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).

CREDIT: MARTY KATZ

actor after revelations that it was leaking hazardous materials.

In a 14 November interview with *Science*'s news staff, Marburger emphasized that "my self-image is as a scientist rather than an administrator." But he also showed plenty of bureaucratic savvy, offering some strong but softly voiced views on what he brings to the task of steering the government's $95 billion research enterprise. He also defended pending changes at OSTP that have drawn criticism from some scientists, and he refuted persistent rumors that his job has been marginalized (see sidebar on p. 1645).

The following excerpts were edited for brevity and clarity by *Science*.

CREDIT: MARTY KATZ

On why he took the job:
The president didn't give me any marching orders. We had a good conversation. I didn't put any conditions on him, and he didn't put any conditions on me. I did not insist on being able to pick up the telephone at any time and talk with him. But I've felt very reassured about accessibility, and I'm quite satisfied with my ability to get things done. I accepted the job after I met the people I would be working with. I liked and respected them. It's a very result-oriented, businesslike Administration, and from my point of view that's very positive for getting things done. If something isn't working, and you come up with a suggestion to make it work better, it tends to be accepted.

On the delay in appointing a science adviser:
They did pretty well [without one]. I do think that during this period, the links between the White House and the science and higher education communities were weaker than they should be, and I've been working to strengthen those links. So I've spent a lot of time at the National Academies and [in] meetings with scientific societies and higher education groups. I'm responding to virtually all requests to appear at events where I can speak directly to scientists. I've met less with the industrial community, but I'm reaching out to them and trying to understand their issues.

Within the Administration, I've been meeting systematically with middle-level policy-makers to find out their attitudes toward OSTP and how they see the landscape and where I fit in. OSTP is a valued agency, and they are glad to see us back in business with a director. [Some people said] the office has not always been sufficiently responsive, mostly in terms of time; I'm interested in doing something about that.

On OSTP's role:
My philosophy is that OSTP is primarily a broker between the federal government's policy-making and budgeting apparatus and the communities they serve: higher education, industry, and science. The primary source of expertise about the needs and opportunities in these sectors comes from them, not OSTP. The office is really there to bring the agencies together and to tap in quickly to talent and information needed to feed the policy-making process. OSTP shouldn't use its people and expertise to do a lot of in-house analysis and lengthy reports, [because that is what] the agencies, the National Academies, and others are prepared to do.

"I didn't put any conditions on [the president], and he didn't put any conditions on me."

On management:
I come from a strongly administrative background, from universities and national laboratories, where the talent is really on the faculty or at the bench. I've always viewed the administration as a tool, as a service to the faculty. What do university presidents do? They fund-raise. They are the marketing people. I'm carrying that philosophy into OSTP. [My senior staff will be] people who can effortlessly plug into the stakeholders—plug into the White House, Congress, and the agencies—and who have a lot [of] knowledge about how they work.

On OSTP staffing:
I'm putting less emphasis on senior positions. I don't intend to fill all four of the Senate-confirmed associate director positions. In the previous Administration, there was one for science, one for technology, one for national security and international affairs, and one for environment. In my view, pulling those four categories out and doing something special with them was artificial. [It also] created [administrative] stovepipes under those directors, which made it harder to work on issues across the board. This is a relatively small office, and that was an inefficient way of organizing it.

I plan to fill two [of the associate director slots], although I can fill the others later if necessary. I'm handling the environment and national security areas differently, and we'll just have to wait and see how it works. I and my two senior deputies [for science and technology], which I call the directorate, will work as a team. Beneath us will be seven departments, headed by assistant directors, that will cover the spectrum: science, technology development, environment, education and the behavioral sciences, space and aeronautics, information technology and telecommunications, and national security. I regard the departments as categories of expertise that are available to the directorate as we go about our business of linking scientific expertise with the government's decision-making apparatus. The directorate will also handle crosscutting international issues.

I expect the staff to be the same size, or maybe even larger. We have 60 slots, with maybe 35 or 40 [of those] currently filled. We need more people, because there is lots of business. I don't see a budget problem [hindering expansion] unless we hire very expensive people.

On talking to the president:
I would regard having to talk with the president as an indication [that] something is very seriously wrong somewhere. Under those circumstances, I believe the president would talk to me. For the immediate needs of the office, when it looks like something awful is about to happen to us, I'll usually call up [economic adviser] Larry Lindsey. But when there is some more difficult issue, it's [White House Chief of Staff] Andy Card or [his deputy] Josh Bolton.

On terrorism:
We're very heavily involved in homeland security issues. Coming into the job, I expected to be spending a lot of time educat-

"Explain to Me What I'm Not Getting"

In the 4 months between being chosen by President George W. Bush and confirmed by the Senate, the Washington rumor mill filled with talk of how the White House had downgraded John Marburger's new job. Exhibit A was a change in his title, which dropped an "assistant to the president" tag held by his three immediate predecessors. The whispers also included a long list of perks that he supposedly had lost. But Marburger says it just ain't so.

The altered title "hasn't made a difference," he says. As for the rest, here's his blunt assessment of where things stand: "I have access to a limousine and a driver. I'm on the list for the White House mess [staff dining hall]. I'm going to senior staff meetings. I'm written into presidential directives. People return my phone calls. The things that I've asked for—and I've tried to be reasonable about my requests—I've gotten. I have White House stationery. I have my badge that gets me into the White House. What else do you need? If somebody could explain to me what I'm not getting, I'll be happy to ask for it."

–DAVID MALAKOFF

ing myself about missile defense, about which I know only what I read in the newspapers. That priority has been displaced by the war against terrorism. The most significant thing that has happened is the creation of the Office of Homeland Security under [former Pennsylvania Governor] Tom Ridge. He has asked OSTP to provide the technical support for his office, and we are doing so. There is a provision in the presidential directive for a senior director for R&D, and currently we are filling that function. [We are also] setting up a network within the agencies and with the National Academies to help us evaluate the thousands of proposals on how to win the war on terrorism that are coming in over the transom. I've met twice now with the senior science people at the agencies to talk about how to organize the agencies to [help] with this issue.

On regulating visas for foreign students:
I've sent a strong and consistent message every time I've met with higher education organizations: Each campus really has to have a dialogue on these issues. Universities have a lot [of] assets to bring to the table in the war against terrorism, but there are also vulnerabilities. They are vulnerable to exploitation by terrorists, and they are also vulnerable to society's reaction, [such as] restrictive regulations. Universities have to be prepared to state what will work and what won't. I certainly carry my [academic] experience into the policy-making circles. And it's very nice to have [former Stanford University provost] Condoleezza Rice as the National Security Advisor; she understands universities and is very interested in this issue.

The president understands the importance of freedom, not just for society at large but also for the functioning of higher education and research. Nobody wants to create conditions that will impair the research effectiveness of the United States [or] create conditions that will make it impossible to get a high-quality education.

On next year's budget:
I arrived late, but yes, I'm deeply involved in the 2003 budget process. I've been in the budget meetings, and I'm providing advice. There is widespread recognition that strength in science is a highly important national objective. The president himself has made a commitment to increase the [National Institutes of Health] budget. He is very interested in math and science education. There is concern throughout the agencies and OMB [the White House Office of Management and Budget] about balance and making sure that the physical sciences don't get left behind. That is very much on my mind. Although it is obvious that the war on terrorism is expensive and there is a global economic downturn, there is a commitment to keep science strong. I don't see a lot of new initiatives, [but] I can't be much more specific.

I'm not uncritical of how science tends to ask for money. I'd like to try to get some feedback about how to do that more effectively. In general I don't like arbitrary formulas, like "let's double or triple" an agency's budget. That doesn't work well in the long run. You've got to have a reason for doing that.

On avoiding duplication:
If there are two agencies trying to do the same thing, I get them together and we work it out. It works much better than I expected. I've been an outsider looking in at a sort of impenetrable maze of working groups and crosscutting committees. Now I can see it from the other side, and these groups actually work and crosscut! One thing that helps is that I've been working very closely with [OMB, which sets budgets and oversees spending]. There is nothing like OMB to help straighten out turf issues between agencies.

"There is concern ... about balance and making sure that the physical sciences don't get left behind."

On research infrastructure:
There is an infrastructure problem. The problem of aging facilities is probably greater than the need for new facilities. But exactly how to do something about that is a rather complicated policy matter. There could be a facilities initiative of some kind, or it could be something involving strategy with facilities and administration cost recovery. That discussion is open.

On judging his performance:
That's a hard question to answer, because so much of what I do is preventing disasters, fixing things, or gaining access. [Members of the community] need to see science being taken seriously by the agencies and the Administration. They need to see rational budget proposals. They need to see action, which includes [incorporating] science at the highest levels of national decision-making. I don't guarantee miracles.

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