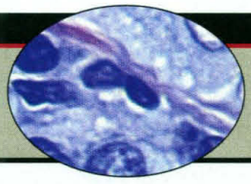
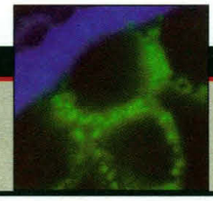


1475
Cancers that build their own blood supply

LEAD STORY 1476
Visionary research at the Pentagon

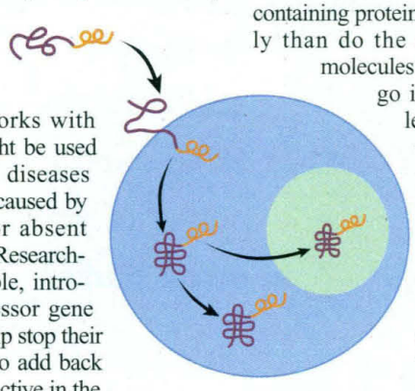


1481
Plant biotech for the developing world

cells. One answer is to coax the target cells to make the protein themselves, by inserting the corresponding gene, but so far no one's figured out how to deliver nucleic acids efficiently to cells in animals or humans. Now researchers may have hit on a powerful strategy: fusing foreign proteins to a segment of another protein, derived from the AIDS virus, that has an unusual ability to cross cell membranes.

On page 1569, molecular biologist Steven Dowdy of Washington University School of Medicine in St. Louis and his colleagues report that such tagged molecules can infiltrate all the tissues of living mice. "This is an entirely novel and apparently powerful approach for introducing proteins into the brain and throughout the body," says Raymond Bartus, a neuroscientist at Alkermes Inc. in Cambridge, Massachusetts.

If the method works with other proteins, it might be used to combat inherited diseases and other conditions caused by a malfunctioning or absent intracellular protein. Researchers might, for example, introduce a tumor suppressor gene into cancer cells to help stop their abnormal growth or to add back the enzyme that's defective in the hereditary neurodegenerative disease, Tay-Sachs disease. "It really is intriguing and unexpected … that you can get proteins so pervasively into cells," says Bert Vogelstein, a cancer geneticist at Johns Hopkins University School of Medicine in Baltimore. Still, Bartus cautions, "a lot of the details have to be worked out, and it will take some time before [the method] is harnessed for therapy in humans."



Shipping tag. Once the TAT sequence (orange) helps a partially unfolded protein enter a cell, the protein refolds and becomes active.

To devise the method, Dowdy and his colleagues exploited the 10-year-old discovery that an AIDS virus protein known as TAT (for trans-activating protein) enters cells without aids such as cell surface receptors. Researchers don't know how TAT does that, but in 1994, investigators at Biogen in Cambridge, Massachusetts, showed that it could ferry other proteins into cells. They chemically attached a bacterial enzyme called β-galactosidase to a large piece of TAT that included its "protein transduction domain" (PTD), a stretch of 11 amino acids that helps TAT traverse the cell membrane. When they injected the cross-linked protein into mice, they detected hints of its presence in several tissues. "[The method] was inefficient, but it did work," Dowdy recalls. "We thought to ourselves, 'This has tremendous merit' and picked up the literature trail."

To try to improve the efficiency, the group took what Dowdy calls a "biochemically blasphemous" approach. Unfolded, "denatured" proteins lose their activity. But reasoning that a partially unfolded protein would have more of its oily interior amino acids exposed and might therefore slide more easily through the lipid-rich cell membrane, the researchers denatured test proteins that carried the TAT PTD before incubating them with cultured cells. As the group reported last December in *Nature Medicine*, denatured PTD-containing proteins enter cells more efficiently than do the native versions. "Other molecules in the neighborhood don't go in, and nothing appears to leak out," says Dowdy. But with the denatured protein and its attached PTD, "it's like the parting of the Red Sea. No one knows how it happens."

The group has used this strategy to transport over 50 proteins ranging widely in size into a variety of human and mouse cell types in culture. Once inside, they regain their activity, presumably because they can access the cell's normal protein-folding machinery, says Dowdy. Now the team has extended the method to live animals.

Steven Schwarze, a postdoc in Dowdy's lab, engineered a protein that contains the PTD from the TAT protein attached to β-galactosidase. After partially unfolding the protein, the team injected it into the abdominal cavities of mice, while control animals got a version without the TAT sequence. Four hours later, the researchers found little or no detectable β-galactosidase in the tissues of the controls. But the protein joined to the TAT PTD showed up throughout every tissue they looked at—blood, spleen, liver, kidney, heart, lung, and even brain—and it had regained its enzymatic activity. "Not only do you know that the whole protein got in, but you know it refolded properly," says Joan Brugge, a cell biologist at Harvard Medical School in Boston.

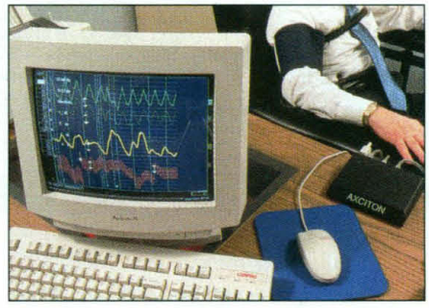
The technique should give basic researchers an extremely efficient way of introducing proteins into cultured cells to see how they affect cell function. And ultimately it might be used in treating human diseases as well. But as Bartus and others point out, there are potential pitfalls. The PTD could elicit an immune response or the method could produce other toxic effects, although no signs of problems have appeared yet. And the very efficiency of the method could cause trouble. "One important issue is that if there's a spill, the aerosol could be taken up by the lungs and then spread quickly in the body," Brugge says. "So for experimental use, investigators have to be really careful."

Dowdy says that it probably won't be possible to target proteins carrying the TAT PTD to particular cells, but the group has already begun to cope with the delivery system's promiscuity by designing proteins to act only in certain cellular environments. As scientists tune the basic scheme, they'll no doubt find many ways to help proteins reach their full potential. **–EVELYN STRAUSS**

SCIENTIFIC COMMUNITY

DOE Polygraph Plan Draws Fire

The Department of Energy (DOE) has moved a step closer to subjecting up to 5000 researchers and other employees at its three nuclear weapons laboratories to lie detector tests. The long-awaited proposal, published in the 18 August *Federal Register*, has triggered protests from opponents—including a petition by 165 Los Alamos scientists—who say that the devices aren't reliable and that testing could damage morale and recruiting efforts. While DOE has scheduled hearings on the plan, both sides say that expanded use of the polygraph seems to be an inevitable consequence of allegations that China has obtained secrets about the U.S.



Truth or consequences. DOE pushes ahead with polygraph plan for weapons labs.

CREDITS: (TOP TO BOTTOM) CARIN CAIN; MARK C. BARNETT/PHOTO RESEARCHERS

nuclear arsenal.

Critics "can write all the petitions they want, but [polygraphs are] coming," says DOE counterintelligence chief Ed Curran. However, he notes that the current proposal is the product of negotiations with lab managers and staff and that DOE has no desire "to force testing down people's throats." Chris Mechels, a retired Los Alamos computer scientist and vice president of the Los Alamos National Laboratory Employee Rights organization, also doubts the tests can be derailed. With Congress backing the plan, opponents can make "obligatory protestations, but I think it's a done deal," he says.

DOE chief Bill Richardson outlined the polygraph plan in April as part of a suite of security measures designed to calm members of Congress alarmed by allegations of Chinese espionage at Los Alamos, Lawrence Livermore, and Sandia national laboratories (*Science*, 26 March, p. 1986). Before the plan is put in place, however, the agency must collect public comment on how it plans to treat the 20,000 nonfederal employees who make up most of the lab staffs. They work for the University of California, which operates the Los Alamos and Livermore labs, and for the Lockheed Martin Corp., which operates Sandia.

The *Federal Register* notice (www.access.gpo.gov/su_docs/fedreg/a990818c.html) fills in the blanks. It specifies eight groups of employees and job seekers who would be "eligible" for periodic testing, including those involved in counterintelligence work and research that requires access to classified data. Overall, more than 10,000 lab employees would fall into one of the groups, but DOE officials say most lab scientists, whose work is not classified, would not be included. The proposed rule notes that the exams are voluntary, but that those who decline them could face "consequences," including loss of their security clearance and transfer to a less sensitive position. The plan also gives test-takers 48 hours notice, but does not allow a lawyer or witness to observe the questioning. DOE officials say examiners will be limited to asking four "yes or no" questions related to spying and sabotage. "We did everything we can do to give the advantage to the person taking the polygraph," Curran adds.

In the notice, DOE "acknowledges that some individuals consider polygraph examination results to be generally unreliable," but contends that there are "no scientific studies" that cast doubt on their value "as an investigative tool." Indeed, the agency claims polygraph results "are superior to random interviews" but should not "constitute the sole basis for taking any action against an individual." The notice also disputes critics who say testing could drive away researchers, and Curran told *Science* that less than half of those eligible will probably be tested.

Such assurances are small comfort to lab employees. Some are signing up to speak next month at a series of public hearings on the proposal, while others are signing petitions. The resisters include 165 members of Los Alamos's X-Division, which does top-secret work on nuclear weapons. "We are opposed to unwarranted blanket polygraphing of Q-cleared personnel," the petitioners wrote to Richardson last week, referring to a security clearance that gives holders access to classified information on a "need to know" basis. DOE officials say such blanket exams are not under consideration.

At Livermore the alarm is being raised by the Society of Professional Scientists and Engineers, an employees organization. "If thousands of workers are tested, as DOE proposes, some will surely be falsely accused of lying, with devastating effects on their careers," says computer scientist Patrick Weidhaas. It is "unthinkable," he says, that a "research institute with top scientists is supposed to undergo testing using a machine that a lot of experimentalists would not want to have in their lab due to its lack of accuracy." –DAVID MALAKOFF

SCIENTIFIC COMMUNITY

Salk Institute President To Step Down

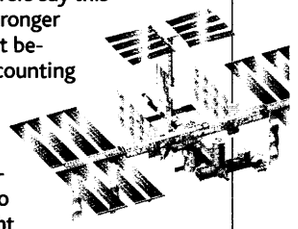
LA JOLLA, CALIFORNIA—Three years ago, the appointment of cell biologist Thomas Pollard to head the Salk Institute for Biological Studies here ended a long and tortuous search for a leader to help put this scientifically rich, but endowment poor, institution on a more solid financial footing. Pollard has done that—Salk's endowment more than doubled, to over $100 million, during his tenure—but the leadership vacuum returned last Monday, when Pollard announced that he would step down as the Salk's president next year.

The reasons are murky, although trouble for Pollard was evident as early as February, when the institute split his job, leaving him as president but giving the CEO responsibilities to board chair Frederick Rentschler. "Being president is tough at a place like the Salk, where you have to administer it and raise money," says Stephen Heinemann, chair of the academic council. Pollard, he says, "actually has accomplished a number of things," but Heinemann stresses that "what makes Tom most enthusiastic is when he's doing his science." Pollard himself says he wants to spend more time in his lab. "If there were 36 hours in every day, it would have been easier," says Pollard, who plans to stay on as a Salk faculty member.

The Salk has a stellar research faculty but lacks alumni, an attached medical school, or a famous president—all aids to fund raising.

ScienceScope

Tilting at Solar Panels? Opponents of the international space station are staging another budget raid. Representative Tim Roemer (D–IN) announced last month that he will attempt to redirect $2 billion from the station's 2000 budget to other programs. Similar bids have failed in the past, but observers say this year's push packs a stronger political punch, in part because the General Accounting Office recently concluded that NASA still doesn't know the station's total price tag, adding to cost worries. Also, tight budgets in other programs have lawmakers hunting for funds; they have already "borrowed" $1 billion from NASA's 2000 budget. Finally, Roemer has forged alliances with veterans and fiscal conservatives, who have lobbying muscle.



The vote—expected on 8 September—"could be much closer than we would prefer," predicts one pro-station House aide. And "victory or not," it will highlight the project's flaws, says critic Ralph DeGennaro of Taxpayers for Common Sense, who charges that "the station is not science, it's science fiction."

The One-Night Standard One night of passion with that seductive foreigner you can keep to yourself, but two and you've got to tell—even if you can't remember their name. That is the gist of a recent Department of Energy (DOE) security memo that has some researchers amused.

Last month's counterintelligence directive spells out when DOE staff and scientists have to report "close and continuing contact" with citizens of "sensitive" nations, such as China, India, and Russia. It notes that employees can stay mum about one-night stands, so long as the pillow talk avoids secret subjects. But "if personnel have ... intimate contact on more than one occasion with the same foreign national ... the relationship must be reported" to security officials. And a lust-clouded mind is no excuse: "Such contact must be reported regardless of whether the foreign national's full name and other biographic data are known."

DOE officials say the policy is nothing new and is designed to avoid unnecessary intrusions into privacy. But one of the agency's globetrotting researchers says it is "a bit more explicit" than past guidance. In particular, he jokes, "it's a relief to know you don't have to remember your bedmate's name to comply."

CREDIT: DOUG STEVENS