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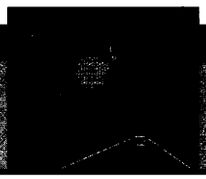

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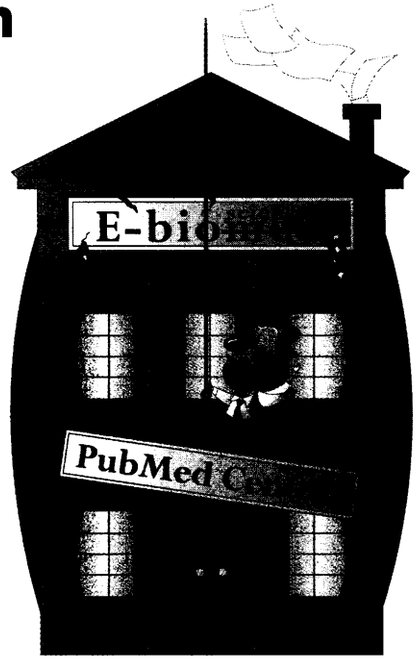
SCIENTIFIC PUBLISHING

NIH's Online Publishing Venture Ready for Launch

It's time to stop talking about a free, public Web site for life science articles and start building one, says Harold Varmus, director of the National Institutes of Health (NIH). This week, Varmus announced that NIH will launch its electronic archive and publication site, now called PubMed Central (formerly E-biomed), beginning in January 2000. It will accept reports—both reviewed and some unreviewed material—comments, and data files from journals and scientific groups and redistribute them on the Internet at no charge. The final plan is described in a notice released by NIH on 30 August (www.nih.gov/news/pr/aug99/od-30.htm).



The Web site also gained one of its first major recruits last week: the American Society for Cell Biology (ASCB). According to ASCB director of publications, Heather Joseph, the society's council voted to share the complete contents of ASCB's journal, *Molecular Biology of the Cell*, with a 2-month delay after publication, "on an experimental basis." Joseph explains, "We very strongly support the goal of barrier-free access to the scientific literature" and want to help NIH's "laudable" effort. Commercial journals have not shown any interest in donating text, however, and many nonprofit journals remain ambivalent. Although the plan would allow journals donating material to charge authors a fee, some editors and publishers worry that, if they do, they will drive away authors and ultimately lose revenues. Some, including *The New England Journal of Medicine* and *Science*, have published editorials criticizing NIH's plan as monopolistic and not adequately supportive of peer review (*Science*, 9 July, p. 197).

But Varmus believes the chilly reception does not reflect the views of rank-and-file scientists. In an interview with *Science*, he said: "Some major journals that have very little to lose here have been incredibly resistant," although "we've had a productive discussion" about how to make scientific data more widely available. He added, "I have heard less from the scientific community than I am used to, because people in the trenches are used to having their opinions bubble up through their leaders, and [in this instance] some of their leaders have been a little resistant." Varmus seems convinced that the best way to test the concept is to launch it.

"To focus the next step," Varmus says, NIH will establish an Internet server called PubMed Central, which will be linked with the popular citation and abstract database, PubMed, run by the National Center for Biotechnology Information. "Any journal that wants to provide its content at any time after acceptance—and it doesn't have to be reviewed acceptance—can do so," he says. PubMed Central will accept contributions long after publication, "even a year later." The server will share its content on a daily basis with mirror sites in other countries. Varmus estimates the annual cost to NIH will be very low, $1 million to $3 million.

The only other group that so far has indicated it may be ready to join NIH in distributing reports electronically is the European Molecular Biology Organization (EMBO) in Heidelberg, Germany. Encouraged by EMBO's executive director, Frank Gannon, EMBO and its affiliates have been discussing plans to create a life sciences data center with about a dozen scientific groups. At a meeting in July, they drafted a set of principles for "E-bioscience," a name they preferred to "E-biomed" because they envisioned a broader site, encompassing all life sciences.

Varmus says NIH has also broadened its proposal to embrace the nonmedical life sciences, a change initiated partly in response to comments from the community. In addition, to allay concerns that a government organization will have too much power over the content of PubMed Central, NIH is taking steps to minimize its editorial role: "Nothing that goes on the server will be determined by NIH," he says. Instead, NIH will act as gatekeeper, accepting both peer-reviewed work and material that has only been "screened but not formally peer reviewed"—but only from approved groups. At the moment, NIH has some "very stringent" provisional rules limiting the kind of groups that may provide screened-only material. But Varmus is asking the National Academy of Sciences to create an international advisory body that would assume responsibility for deciding who should be allowed in the gate.

The academy could also help in another way—by contributing text from its own journal, the *Proceedings of the National Academy of Sciences (PNAS)*. Nicholas Cozzarelli, editor of *PNAS*, strongly supports public sharing of *PNAS*'s content and has asked for authority to send material to NIH's new data center. The academy's governing council considered the request last month and deferred to the publications committee, chaired by vision researcher Lubert Stryer of Stanford University. Stryer says that in general, "I favor PubMed Central." His committee will take up the matter on 13 September.

If the academy decides to donate full-text material from *PNAS*, Varmus will have won an important symbolic battle in his effort to establish the credibility of PubMed Central.

–ELIOT MARSHALL

CELL BIOLOGY

Introducing Proteins Into the Body's Cells

To pharmaceutical chemists and basic researchers, proteins are a bit like protégés who never quite fulfill their potential. Despite their wealth of biochemical talents, they generally lack the one skill scientists need to put those talents to work: the ability to make their way through the fatty membrane that surrounds

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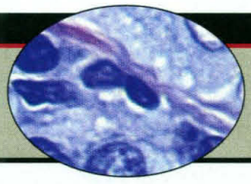
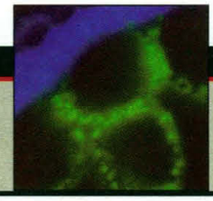


1475
Cancers that build their own blood supply

LEAD STORY 1476
Visionary research at the Pentagon

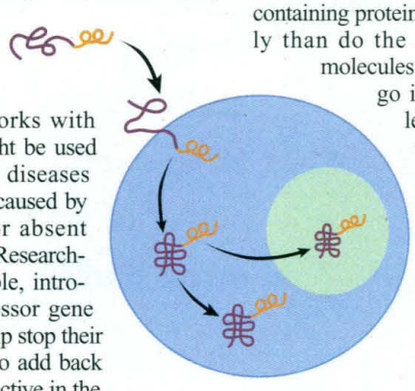


1481
Plant biotech for the developing world

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.

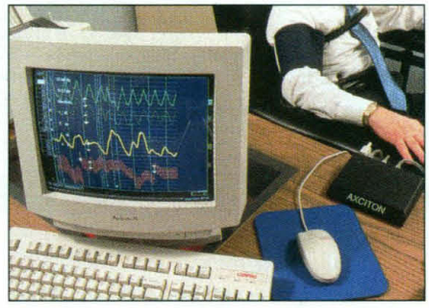
The technique should give basic researchers an extremely efficient way of introducing proteins into cultured cells to see how they affect cell function. And ultimately it might be used in treating human diseases as well. But as Bartus and others point out, there are potential pitfalls. The PTD could 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.

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