"Abzymes" Make Their Mark?

Mother Nature does not always provide biochemists with all the tools that they would like to have. They would say she has been lax, for example, in supplying the enzymes that they need for dissecting protein structure and function. On page 1188 of this issue of *Science*, Kim Janda, Diane Schloeder, and Richard Lerner of the Research Institute of Scripps Clinic in La Jolla, California, and Stephen Benkovic of Pennsylvania State University in University Park report a new development that may help overcome this deficiency.

The development is another step on the road to producing antibodies that can act like enzymes in speeding up chemical reactions. Whereas naturally occurring protein-splitting enzymes have a rather restricted range of specificities, the antibodies used by the immune system to fight off disease have virtually unlimited specificities. The goal is to tap the unlimited diversity of antibodies to generate designer enzymes with any specificity that a researcher wants.

In the current work, Janda and his colleagues have produced a catalytic antibody that can split the amide bond. The peptide bond that holds amino acids together in proteins is a type of amide bond, and the research opens the door to producing catalytic antibodies that cut proteins at specific sites.

Not only would such antibodies be valuable in basic research on proteins, but they might also have medical applications, such as searching out and destroying tumor cells or blood clots.

Two years ago, the Lerner group and also that of Peter Schultz at the University of California at Berkeley showed that antibodies can split ester bonds (*Science*, 19 December 1986, p. 1497). The amide bond is a much tougher nut to crack, however. It requires roughly 10,000 times as much energy to split as an ester bond, although this figure will depend on the chemical makeup of the compounds being compared. "The amide bond is a sort of gauntlet that chemists and practical-minded people throw down," Lerner says. The new work shows that catalytic antibodies, or "abzymes" as they are sometimes called, can match natural enzymes in performing difficult chemical tasks.

To generate the amide-splitting antibody, Janda and his colleagues used the same general approach that they had previously used for the ester-splitting abzyme. This involves using a compound with a structure resembling that of the transition state of the reaction to be catalyzed as an antigen for generating production of monoclonal antibodies.

The transition state is a high-energy intermediate through which the starting compounds of a reaction must pass to form products. The idea is to produce an antibody that can bind to and stabilize the transition state, thereby speeding up reaction, in this case the amide hydrolysis.

One of the 44 monoclonal antibodies that the researchers eventually tested on their experimental amide proved to be very effective in this regard. It speeded up the hydrolysis by a factor of about 10^5. This puts it in the same ballpark as natural enzymes. "The increase was much larger than we expected," Benkovic says. "Now we have to find out what the mechanism [of the reaction] is."

The large increase that occurs in the reaction rate suggests that the catalytic antibody may have been doing more than just stabilizing the transition state for the reaction. It may have been taking a more active role, perhaps putting stress on the amide bond to make it break more readily. Alternatively, some of the amino acids in the antibody may participate directly in the reaction by contributing an acidic or basic group.

Discovering how the catalytic antibody works is important, Benkovic says, because the information will be helpful in future efforts to generate catalytic antibodies. "We have to learn to deliver the right message in the antigen to get antibodies with high catalytic activity," he points out.

Natural enzymes are noteworthy for their specificity as well as for their speed—and the amide-splitting antibody passed muster in this regard, too. A small change in the amide structure not only prevented it from being split by the antibody, but converted it to an inhibitor of the abzyme activity. "Once again the exquisite specificity of antibodies is being played out here," Lerner says. The next challenge is to generate antibodies that cut peptides themselves. ■ JEAN L. MARX

Fetal Panel to Meet

The National Institutes of Health has created a special panel to examine the ethical, legal, and scientific issues surrounding the therapeutic use of fetal tissue from induced abortions. The panel, which will meet at NIH 14 to 16 September, will advise the government on whether this work should be allowed, and under what circumstances.

Experiments using intentionally aborted fetal tissue were banned last March, after Assistant Secretary for Health Robert Windom reviewed an NIH research proposal to use fetal tissue transplantation as a therapy for Parkinson's disease. The ban has engendered concern among researchers who view fetal tissue transplants as a promising, if speculative, approach to the treatment of Parkinson's disease, diabetes, and perhaps other diseases.

What the Administration is concerned about is abortion—specifically, whether the fetal tissue comes from an intentional abortion. The temporary ban does not apply to experiments using fetal tissue from spontaneous abortions or stillbirths, though Windom has asked NIH to reexamine those procedures as well. The medical use of fetal tissue, from any source, is already tightly regulated by both federal and state law.

Windom sent a long list of questions for the NIH panel to consider, including whether the use of fetal tissue in research will encourage women to have abortions they otherwise would not, and whether abortions will be intentionally delayed so that a second trimester fetus will be available. Windom also wants to know if the demand for fetal tissue is likely to grow—and if so, what the effect might be on abortion practices.

On the scientific side, the questions are chiefly: Does this approach work? Have there been adequate animal studies? Is it applicable to others disorders? And what is the likelihood that advances in fetal cell culture will provide an alternative to fresh fetal tissue?

Arlin Adams, a retired judge of the U.S. Court of Appeals, is the chairman of the 18-member panel. Leroy Walters of Georgetown University will chair the sessions on ethics, and Kenneth Ryan of Harvard University will chair the scientific sessions.

For Ryan, it is the second time around on some of these questions. He chaired the 1972 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which concluded that aborted tissue, from dead fetuses, could be used for medical purposes under the Uniform Anatomical Gift Act.

■ LESLIE ROBERTS