NEW STRUCTURAL DETERMINATION OF CATALYTIC ANTIBODY COULD LEAD TO IMPROVEMENTS IN SPEED AND EFFICIENCY

La Jolla, CA. — Scientists at The Scripps Research Institute (TSRI) in La Jolla, California, have developed new insights into the structure and mode of action of catalytic antibodies—antibody proteins with enzyme activity—that could improve the speed and efficiency of these proteins in catalyzing chemical reactions and thus their value to the pharmaceutical and chemical industries.

By comparing the three-dimensional structures of an antibody and a natural enzyme that both catalyze the same chemical reaction, they have shown that the mechanisms of catalysis for both proteins are very similar. Based on these observations, they can begin to fine-tune strategies for developing catalytic antibodies with activities approaching those of natural enzymes.

The study, entitled Routes to Catalysis: Structure of a Catalytic Antibody and Comparison with its Natural Counterpart appeared in the February 4 issue of Science. Its authors are Matthew R. Haynes, Enrico A. Stura, Donald M. Hilvert, and Ian A. Wilson. Haynes is a graduate student in Dr. Wilson’s laboratory; Drs. Stura and Wilson are in the Department of Molecular Biology at TSRI, and Dr. Hilvert holds appointments in the departments of

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The feasibility of developing antibodies with catalytic properties was pioneered at TSRI in the late 1980s. Combining techniques and principles of chemistry, molecular biology, immunology, and genetic engineering, this technology holds the promise of developing catalysts for many thousands of chemical reactions.

The technological implications of this vast pool of potential antibody catalysts are enormous. For example, many of the chemical reactions used today to produce pharmaceuticals and other valuable compounds are difficult and expensive to run and produce low yields of product. Indeed, some reactions chemists would like to carry out on an industrial scale are simply not feasible. With the right antibody catalysts, however, these same reactions could be made to run swiftly, with great precision, and in high yield—much in the same way that biological reactions occur in the presence of enzymes.

Catalytic antibodies are prepared by raising antibodies in animals against synthetic compounds called transition state analogues. As bonds are made or broken in chemical reactions, there is a point at which the components of the reaction exist in an intermediate configuration where the reaction could go either way. This molecular configuration, called the transition state of the reaction, has a fleeting existence and cannot be isolated. However, chemists can deduce what the transition state of a particular reaction must look like and create compounds with very similar shapes—transition state analogues.

Enzymes catalyze or accelerate chemical reactions by binding these transition states and stabilizing them, thereby increasing the likelihood that the reaction will occur. Similarly, antibodies that can bind to transition state analogues can also bind the corresponding transition states themselves. Thus, they too catalyze chemical reactions.
Unfortunately, the majority of the catalytic antibodies generated to date possess but a small fraction of the chemical activity of natural enzymes. It is a serious problem; in order to be useful in biotechnological and industrial applications, catalytic antibodies will need to have far greater activity.

To approach this issue, the TSRI investigators made a direct comparison of the three-dimensional structures of a catalytic antibody and an enzyme that carry out the same chemical reaction. By so doing, they hoped to gain insight into the precise nature of catalysis by these different proteins, and the particular architectural features of the catalytic surfaces that accelerate the chemical reaction.

The system they chose to study involves a chemical reaction in plants and bacteria that is integral to the synthesis of certain amino acids. Specifically, it is the conversion of the compound chorismate to prephenate, an event catalyzed by the enzyme chorismate mutase.

For the past several years, Dr. Hilvert and his colleagues at TSRI have carried out detailed studies of a number of catalytic antibodies elicited against a transition state analogue of the chorismate-prephenate reaction. Using the technique of x-ray crystallography, Haynes and Drs. Stura and Wilson determined the complete three-dimensional structure of one of these catalytic antibodies with the transition state analogue bound to the catalytic site.

For comparison, they used the three-dimensional structure of the enzyme chorismate mutase, also bound to the same transition state analogue, which recently had been published by investigators at Harvard University. The chorismate catalytic antibody has about one ten thousandth the catalytic activity of the natural enzyme.
A study of the two structures, antibody and enzyme, showed that both appear to catalyze the reaction in essentially the same way. This finding refutes the suggestion by some scientists that although enzymes and catalytic antibodies both may be able to carry out the same chemical reaction, the precise mechanisms of catalysis may not be the same.

Also of major importance was the identification of those structural features of the enzyme that most likely account for the much greater activity of the enzyme as compared to the antibody. This information, they suggest, can now be used to dramatically improve the catalytic efficiency of antibodies by such strategies as improving the design of transition state analogues and altering the structure of antibody proteins by site-directed mutagenesis techniques.

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