# Chemistry

*Ivan Amato and Janet Raloff report from Dallas at the American Chemical Society's spring national meeting*

## Turning antibodies into chemists

To create exquisitely specific tools for future chemical missions ranging from destroying viruses to building new proteins, scientists have been teaching antibodies to act like enzymes.

Antibodies recognize and bind to particular chemical structures — usually molecular intruders in the body — with a specificity unmatched in the world's molecular menagerie. By luring chemical starting materials, or reactants, and then helping them overcome initial energy barriers, enzymes rapidly trigger thousands of biologically crucial chemical transformations.

Since 1986 scientists have been reporting ways of conferring the reaction-speeding skills of enzymes to antibodies, which also specifically bind reactant molecules while ignoring all others. Most efforts so far have involved making stable molecular analogs that chemically resemble a reaction's so-called "transition state," a fleeting molecular structure chemists believe must form before reactants can change into products. By injecting these analogs into mice, scientists can use the animals' immune systems as factories for making catalytic antibodies with binding pockets that custom-fit the actual transition state of the reactant molecules. Once bound in this way, reactants quickly rearrange into products.

Peter G. Schultz of the University of California, Berkeley, reports new tactics for fitting the antibodies' binding sites with additional chemical features that could enable scientists to make many more catalytic antibodies tailored for almost any chemical transformation. In one versatile tactic, Schultz and his colleagues attached a flexible molecular "handle" near the binding site of antibodies. "Now we have an antibody that has a handle on it with which we can presumably introduce any reactive group we want," he says.

Moreover, says Schultz, "we can put reporter molecules on there to make antibodies into sensors." In one example, the researchers attached a fluorescent molecule to the handle. When the particular chemical that the antibody binds docks into the binding site, the fluorescence dims. By monitoring for such changes, the group can infer whether the chemical is present in a sample.

Several scientists report making catalytic antibodies that break the tough amide bond between amino acids, which string together into enzymes and other proteins. Without enzymatic help, seven years would pass before the average amide bond in a protein broke, remarks molecular biologist Richard A. Lerner of the Research Institute of Scripps Clinic in La Jolla, Calif. "Acting as specific chemical scissors, these antibodies may have the ability to cut up a virus or break apart a blood clot," says Kim D. Janda of Scripps. He reports making antibodies that can cut about three specific amide bonds in an hour. Although improvement must precede their application, such antibodies could enable scientists to cut and paste strings of amino acids into virtually any sequence to make new proteins, says Lerner.

## Pediatric peptide spurs growth hormone

Growth-hormone deficiency afflicts about one in every 5,000 infants in the United States. Untreated, these children will grow up to be 7 to 10 inches shorter than normal. Physicians currently treat the deficiency by injecting genetically engineered growth hormone every few days for up to 10 years during a child's critical growth period. But a new drug may someday help many children achieve normal stature by producing the hormone on their own. And in the barnyard, a closely related chemical may yield important dividends of another sort.

About 80 percent of children with the deficiency are physiologically capable of supplying the growth hormone themselves, estimates Arthur Felix, who heads peptide research at Hoffmann-La Roche Inc. in Nutley, N.J. What they need are sufficient amounts of the 44-amino-acid peptide that normally triggers the pituitary gland to secrete the hormone. Hoffmann-La Roche has now synthesized this peptide, called growth-hormone releasing factor (GHRF).

Felix says GHRF supplementation might offer several advantages over conventional growth-hormone therapy. Containing fewer than one-fourth the amino acids of human growth hormone, GHRF is much simpler to make. Its smaller size also suggests parents may eventually be able to administer it by nasal spray or dermal patch — techniques children are likely to prefer. Moreover, GHRF treatment would allow the body to generate the whole family of growth-hormone compounds normally secreted, not just the single form provided by hormone therapy today. Finally, the body has a feedback mechanism that will shut off its own GHRF production when growth-hormone levels get too high. This suggests, Felix says, that the body might naturally compensate for any small GHRF overdose, whereas it cannot limit excess growth hormone. Hoffmann-La Roche has just begun using the GHRF peptide in a clinical trial expected to involve about 50 children.

The similarity between growth hormone in humans and in many other species led Felix's team to explore livestock applications of the GHRF as well. In a series of just-completed studies, the researchers injected lactating cows and pigs with a 29-amino-acid analog of the pediatric drug's most pharmacologically active region. The shorter analog not only provided a range of benefits but also proved 5 to 10 times more potent than the 44-amino-acid parent compound. In a 10-day study involving 15 holsteins, those receiving daily injections of the analog produced 15 to 20 percent more milk than did untreated animals. In a 60-day trial involving 75 male pigs, changes were even more striking. Compared with untreated animals, pigs getting the GHRF analog gained 15 percent more weight per pound of feed. The composition of their meat changed, too: They put on 15 percent more muscle and about 25 percent less fat. What's more, says Felix, their meat showed a decline in the ratio of saturated to unsaturated fats.

The team is now working to develop a longer-acting form of the livestock drug, perhaps requiring injection only once every 30 to 60 days. For pediatric use, their eventual goal is a similarly small, high-potency analog.

## Making plastics visible to X-rays

Polymer chemists have discovered that a chemical additive long used as a fungicide in hospital paints and as a flame retardant could also make plastic guns and polymeric medical implants visible with X-ray screening equipment. Guns made of plastic composites containing the additive would be more difficult to smuggle through security checkpoints, and doctors and dentists would be better able to keep track of plastic implants without taking invasive measures, notes Johannes Smid of the State University of New York at Syracuse.

When mixed in a roughly 3:1 ratio with any of a wide variety of commercial polymers, including Plexiglas and polyvinyl chloride, the additive — triphenyl bismuth — makes the composite as X-ray-visible as aluminum, Smid says. Most other additives available for this purpose cannot be used in as many plastics and render the composites X-ray-visible only at the expense of other material properties such as strength, moisture resistance, stability and ease of processing. Moreover, composites of triphenyl bismuth and Plexiglas remain transparent. This, notes Smid, suggests "such plastics can also be used as screens for windows to prevent penetration of X-rays."



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