INDUSTRIAL/ACADEMIC COLLABORATION

RESEARCH CENTER BRINGS ENZYMES TO THE FORE

EXETER, U.K.—Chemists at the University of Exeter, together with microbiologists and biochemists at the Universities of Warwick and Kent, have formed an interuniversity Biotransformations Center. Supported equally by public and private funds, the center will develop the potential of enzymes and microorganisms as substitutes for traditional synthetic techniques used in the chemical and pharmaceutical industries.

In particular, university scientists are seeking to establish the advantages of enzymes in the production of optical isomers of complex organic compounds. By working in "reverse," they will also explore using enzymes that normally break carbon-carbon bonds to synthesize them instead. A third focus will be on oxidases and dehydrogenases—enzymes involved in oxidation and reduction.

Industry is still being cautious about biotransformation, says Stanley Roberts—who recently left Glaxo (Greenford, Middlesex) to head organic chemistry research at Exeter University. But an enzyme that could, for example, replace three synthetic steps and at the same time produce a homochiral (optically pure) compound could be very attractive.

The precise nature of the center's core projects is being kept under wraps. Seven were chosen from 20 put forward to a management committee on which all the industrial sponsors sit. The 10 sponsors—including Glaxo, Beecham (Brentford, Middlesex), ICI (London), and Shell (London)—have each agreed to pay $80,000 toward the projects over three years: Matching funds are provided by the Department of Trade and Industry and the Science and Engineering Research Council on a 50:50 basis.

Companies are also free to sponsor postgraduates or postdocs to work on specific, confidential projects supported by matching public funds. In all, the Biotransformations Center—which has been set up under the U.K. government's LINK scheme to encourage collaboration between industry and universities—already has been guaranteed about $1.8 million for its first three years.

Pressure is increasing to resolve pharmaceutical compounds into their optical isomers for testing and marketing (only one optical form of thalidomide was responsible for its terrible side effects). Moreover, even if harmless, one of a pair of isomers is likely to be biologically inactive and therefore worthless bulk. For example, after discovering a new and very potent inhibitor of herpes viruses, Roberts and his colleagues at Glaxo were able to produce one optical isomer using a nucleotidase and the other with a phosphatase, and recently showed that one isomer was at least 1,000 times more active as a viral inhibitor.

Some evidence already exists of the potential of the oxidases and dehydrogenases—another focus of the new center. One example is the use of the dehydrogenases contained in the fungus Mortierella ramanniana to make optically active precursors to prostaglandins and leukotrienes. But the center will explore other possibilities as well, including oxidases working in oxygen-carrying fluorocarbon solvents. And of the enzymes that might be used in "reverse" to synthesize carbon-carbon bonds, aldolases are of particular interest to the center because some will control the stereochemistry on adjacent carbons while creating a new carbon-carbon bond.

Even though the projects are not likely to be of immediate commercial value to any of the companies, Roberts is optimistic about what the center can achieve for its sponsors. His optimism is based, in large part, on the example of hydrolytic enzymes, notably lipases and esterases. Purified or in microorganisms, these enzymes have already demonstrated the capability to produce a number of homochiral compounds of commercial value, for example, producing 13-hydroxyoctadecadienoic acid—a naturally occurring mediator of interactions between platelets and endothelial cells—in one optical form by hydrolysis of the racemic acetate with a lipase from the fungus Mucor miehei, and in the other by hydrolysis with lyophilized yeast.

Current research in biotransformations has only scratched the surface. The extent to which natural enzymes can be induced to act on unnatural substrates and in the unnatural direction is not known, nor are the further possibilities opened up by site-directed mutagenesis of the enzymes. Although a growing number of biotransformation reactions are already moving from laboratories into development phases, industry is still feeling its way, says Roberts.

—Peter Newmark