CAREERS

UNITED STATES NIH granting formula frustrates some senior scientists **p.399**

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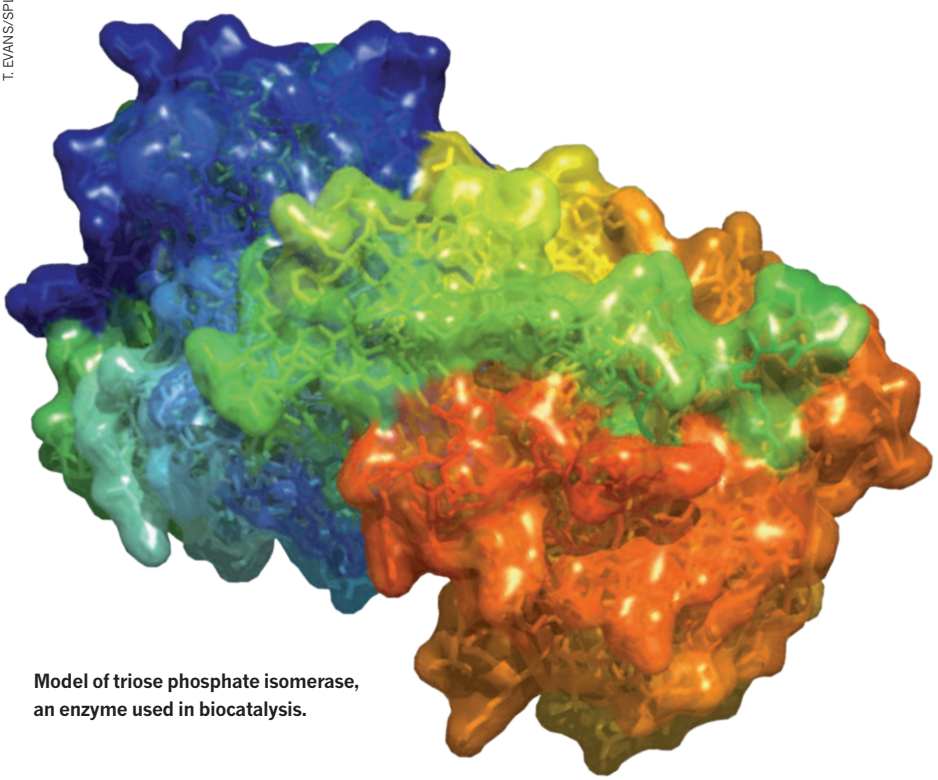

Model of triose phosphate isomerase, an enzyme used in biocatalysis.

CHEMISTRY

Enzyme expertise

Biocatalysis specialists are in high demand in industry.

The global appetite for goods, fuel and pharmaceuticals that are derived from petrochemicals is squeezing the planet dry of resources. Chemists may be able to offer solutions by synthesizing products from alternative raw materials. But one of the most promising avenues in the quest for sustainability may be an amalgamation of chemistry and biology known as biocatalysis, in which biologically produced enzymes are used instead of heavy-metal catalysts to improve the efficiency and sustainability of reactions. Enzymes are gaining popularity in industry, and experts in biocatalysis are becoming hot commodities.

Catalysts are required for chemical transformations ranging from turning a crude-oil mixture into chemicals for manufacturing to making a molecular tweak to a drug candidate. Catalysts are traditionally made from metals such as platinum, rhodium or palladium, with various molecular add-ons designed to help each step of a synthesis. But enzymes can hasten complicated transformations in a single step. By tinkering with enzymes, researchers can coax previously resource-intensive reactions to proceed faster at lower temperatures and pressures, with fewer work-up steps and a higher yield — all of which improves efficiency and saves energy.

Although enzymes cannot replace every catalyst used in industry, they could supplant a great many if companies embrace the technology. Right now, firms seem willing to do this. In the pharmaceutical industry, blighted by thousands of job losses in the past few years, biocatalysis provides a glimmer of hope for scientists seeking opportunities. For example, Novozymes, an enzyme-development company based in Bagsværd, Denmark, has increased its team of scientists from 581 in 2001 to 961 in 2010. And a small biocatalysis group at the research labs of pharmaceuticals giant Merck in Rahway, New Jersey, has survived three rounds of cuts in the past decade, and looks set to remain core to the company's business. Management, says Jeffery Moore, part of that team, "views biocatalysis as a distinguishing feature of chemistry at Merck and a competitive advantage in the marketplace". He adds that because of the lay-offs, most of his recruits are newly redundant chemists, sometimes from Merck, rather than industry new-comers. Competition is tough.

The group at Merck is small — just seven people — but the company also creates opportunities beyond its own confines. "Pharmaceutical companies are outsourcing a lot of synthetic work to lower-cost manufacturers," says Moore. "Where you see a lot of growth in biocatalysis is at those third-party manufacturers."

CATALYSING OPPORTUNITIES

Biocatalysis requires the skills of chemists who can devise synthetic routes to a given molecule; biochemists who can understand enzyme function and reaction conditions; and microbiologists who can engineer the enzymes. There are also increasing opportunities for chemical engineers with an enzymatic bent, says David Rozzell, a consultant based in Burbank, California, who sold his own biocatalysis company, BioCatalytics, in 2007. "I think that the jobs are likely to go up and up," he says. "If the economy improves, I think we're going to see more companies looking to biocatalysis."

Collaborative successes in the past few years suggest that the field has promise. In one case, Merck teamed up with Codexis, an established biocatalysis company based in Redwood City, California, to develop a new enzymatic synthesis for an existing diabetes drug, sitagliptin. (C. K. Savile *et al. Science* **329,** 305–309; 2010) The traditional production route for the drug involves the use of a rhodium catalyst under high pressure, and the product suffers from rhodium contamination. Investigators streamlined the reaction, reducing by-products and lowering costs by around 10%. The enzymatic route also produced only the desired biologically active form of the molecule, rather than the mixture of forms made by the traditional synthesis. The finding could lay the groundwork for similar syntheses of other drugs.

Codexis is also using its expertise in the fuels sector, and has been working with ▶

Shell since 2006 to develop a liquid transport fuel that is not based on petroleum. The company has grown from a staff of 10 when it was founded in 2002 to around 300 today. Two-thirds of employees work in research and development (R&D), says Dawn Kirkland, director of human resources at Codexis. Some 225 employees are based in the United States, but Codexis also has operations in Singapore and Budapest. The company has grown by 10% every year, and currently has 12 openings for scientists. "We tend to hire both PhD scientists and [master's or bachelor's-educated] research associates in the R&D area, and chemical engineers," says Kirkland. Those with PhDs are most likely to be hired as team or project leaders, she says, but there is no expectation that leadership skills be honed before joining the company — an in-house mentoring system, in which senior scientists counsel new recruits, ensures that rookies get the necessary training.

At Novozymes, a commitment to R&D, including the search for new catalysts, attracts specialists, who tend to stay on. At the moment, about 14% of the company's revenue is invested in research, says Nickie Spile, vice-president for global R&D. "That's a lot," she adds. For comparison, in 2009, the world's largest chemical company, BASF in Ludwigshafen, Germany, invested 2.7% of its overall revenue in R&D, and Bayer, based in Leverkusen, Germany, invested 8.8%. Opportunities are global: Novozymes has had sites in China and Japan for 20 years, and in 2010 the company hired around 100 people in Europe alone, says Spile.

Other firms working in the field include Johnson Matthey in London, a traditional-catalyst company that in 2010 bought X-Zyme, a biotech based in Düsseldorf, Germany. X-Zyme's work includes developing biocatalysts that turn ketone and keto-ester molecules into chiral amines, which are used for fine chemicals and drugs. BASF and DSM Pharmaceuticals in Parsippany, New Jersey, both have a strong interest in biocatalysis; BASF employs about 200 scientists in itsR&D unit for "fine chemicals and biocatalysis" (DSM won't divulge its numbers). DuPont of Wilmington, Delaware, is turning to biocatalysts to make propane-1,3-diol, a building block for polymer and plastics.

A CHEMICAL EDUCATION

A career in biocatalysis should start with a solid academic base, and Europe has some strong groups. The University of Manchester, UK, Delft University of Technology (TU Delft) in the Netherlands and Graz University of Technology in Austria are good places to start, says Nick Turner, director of the Centre of Excellence for Biocatalysis, Biotransformations and Biocatalytic Manufacture (CoEBio3) at the University of Manchester. "You need to get yourself into one of those centres," he says. Such institutions offer training, have strong links with each other and with industry, and host many of the big academic names in the field.

In 2009, TU Delft started running a two–year master's degree in biocatalysis. Entrants need a bachelor's-level education; they learn enzymology, proteomics and biocatalysis, and undertake a design project and a three-month placement in industry. And CoEBio3 received a £3.7-million (US$6-million) grant from the European Union (EU) in January to coordinate a project that will train PhD students across Europe for industrial work in biocatalysis. The scheme will be run in conjunction with the EU's Marie Curie training networks, and will initially teach 20 PhD graduates at a time.

Turner says that biocatalysis specialists, even those who concentrate on the biological aspects of the field, need a good grounding in chemistry. There are some biologists at CoEBio3, but it mostly trains chemistry PhD students and postdocs in biotechnical experimental techniques for microbiology, genetic manipulations and protein science. At the moment, around 100 people, including postdocs and PhDs, are working at the centre, but there is scope to grow, says Turner, who hopes to link a selection of EU-based centres of excellence into a pan-European network.

DIRECTED GROWTH

Rozzell says that much progress in biocatalysis in recent years is thanks to techniques such as directed evolution, in which scientists mutate the genes that code for an enzyme, prompting them to produce thousands of variants. The scientists then pick out the variants that will perform best in the desired industrial process: those that work well at a specific pH or temperature, or in the presence of a chemical that the enzyme wouldn't encounter in nature. The technique allows researchers to customize enzymes to fit the ideal conditions for the process.

NOVOZYMES

Scientists in biocatalysis are helping to create a more sustainable future.
Nickie Spile

Directed evolution was pioneered by Frances Arnold, a molecular biologist at the California Institute of Technology in Pasadena, who was Moore's mentor during his PhD studies. Moore says that over the past 15 years, his small group at Merck has switched from a laborious microbiological screening technique to exclusive use of directed evolution. "We can do 100 times the work that we used to do," he says, adding that as the processes become more robust, firms will start to use enzymes to make all sorts of chemicals. Rozzell notes that more and more companies are using directed evolution to produce the enzymes that they then use in large-scale processes.

"It's a field for the future, quite obviously," says Ulf Hanefeld, an organic chemist in the biocatalysis group at TU Delft. He cites the manufacturing process for atorvastatin, a cholesterol-lowering drug now made biocatalytically by Pfizer, as a pharmaceutical success for biocatalysis. "There seem to be plenty of jobs," he says, "but the jobs do require flexibility about where you are based."

One of the biggest motivations to work in biocatalysis, suggests Spile, is that scientists in the field have a sense of purpose, and that they are involved in an activity that could create a more environmentally-friendly future. For the "sustainably-minded chemist", biocatalysis can offer a satisfying career track. Moore agrees. "This is one of the places where I really feel I have an opportunity to change the way the world thinks," he says. ■

COEBIO3

The biocatalysis centre at the University of Manchester, UK, is set to lead a Europe-wide training scheme.

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