Applied Molecular Evolution principals Breitmeyer, Huse, and Bloch surround a benchtop bioreactor.

Biotech gets productive

Biopharma companies know how to make cool stuff. Now they are learning how to make a lot of it. By Stuart F. Brown

THE MANAGER OF A TRUCK PLANT faces hard physical limits to how many vehicles his factory can make in a year. But in the blossoming industry of biotech drugs, where production takes place in a fermenting vat of witches' brew, innovation at the microscopic level can bring huge gains with little increase in costs.

Today a raft of smart ideas—some borrowed from older industries, some still incubating in the research labs, others already at work on the factory floor—promise to give drugmakers a shot at doubling or even tripling output from the same equipment and workforce.

And not a moment too soon. Weighed down by high capital and operating costs, biopharma companies are under the gun to make more stuff more cheaply if the medicines dreamed up by their scientists are to become successful drugs that patients can afford.

Unlike traditional drug companies, which make their products using lab-style

PHOTOGRAPH BY MISHA GRAVENOR

chemical synthesis conducted on a large scale, biopharma grows its medicines in living cells—mammalian, bacterial, or fungal. Protein medicines that are used to treat such diseases as anemia, hemophilia, and diabetes are already a $20-billion-a-year industry. Add the statins that treat high cholesterol (see "The $10 Billion Pill") and the antibiotics that attack infection, and the annual global sales of drugs made in living cells swell to about $65 billion.

Mankind's first foray into biotech drugmaking, if you will, dates back 8,000 years or so to when the Mesopotamians harnessed yeast to transform sugar into the alcohol that makes wine such a restorative drink. About 60 years ago scientists began using fungal cultures to make penicillin and the succeeding generations of lifesaving antibiotics in wide use today. And during the past 20 years researchers figured out how to insert human genes into the DNA of bacteria and animal cells, thereby inducing them to produce therapeutic protein medicines by so-called recombinant means. The first such product was human insulin, produced in 1982 by Eli Lilly & Co. from genetically modified *E. coli* bacteria.

While such fancy genetic manipulation is relatively new, biopharma's development as an industry retraces the history of chemical-drug manufacturing. Both started with chasms between invention and manufacturability. "When the first chemical drug molecules were made, it was for their performance," says Richard DiMarchi, group vice president at Eli Lilly. "Then the industry began to look at how these drugs could be made at lower cost and with greater efficiency. I see that same evolution occurring now on the biosynthetic side."

What unites all biotech drugs is the fermentation processes by which they are made. The plants that produce them are populated by shiny, stainless-steel bioreactors, which are really just high-tech versions of the vats you'd find in a brewery. Inside the bioreactors, cell cultures are provided with the precise nutrient mix and living conditions they need to flourish and produce medicinal molecules.

With dozens of new biotech protein drugs now in the development pipeline, the industry is in a bit of a panic about how to produce them once they clear the FDA's licensing hurdles. The obvious answer is to build more plants full of bioreactors. But these gleaming, aseptic facilities don't come cheap. Charles Cooney, an MIT professor who is an expert in bioprocesses, says it costs about $1,200 per square foot to build and equip a new biotech plant, which adds up to $300 million for a typical 250,000-square-foot facility. What's more, getting a plant designed, built, and approved by the FDA can take four or five years. So rather than just throw more money at the problem by building new plants, the biotech industry is investing a lot of brainpower to make its processes more productive.

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At MedImmune's Frederick, Md., plant, a worker makes a drug that helps premature babies fight lung disease.

MedImmune's plant in Frederick, Md., is a case in point. It's where the $619-million-a-year company produces its flagship product, Synagis, a monoclonal antibody drug that helps prevent lower-respiratory infections in prematurely born babies by marking diseased cells for attack. Synagis is produced in a soupy broth containing genetically modified mouse tumor cells (which are popular microfactories because they replicate so quickly). After MedImmune got FDA approval for the drug and began ramping up production in 1998, the company planned a $100 million plant expansion that would have added a pair of 15,000-liter bioreactors to the two 2,500-liter fermenters already producing the drug. "We were about to break ground and add a lot more stainless steel when our researchers came up with a way to grow the cells at a much higher density in the bioreactors and get them to put out more antibody," says James Young, president of R&D. "We ended up making four times the product we could with the old process, so in effect our 2,500-liter bioreactors instantaneously became 10,000-liter bioreactors."

MedImmune's productivity win, achieved with just a modest R&D investment, is the sort everyone in biopharma is chasing. Although the details are proprietary and jeal-

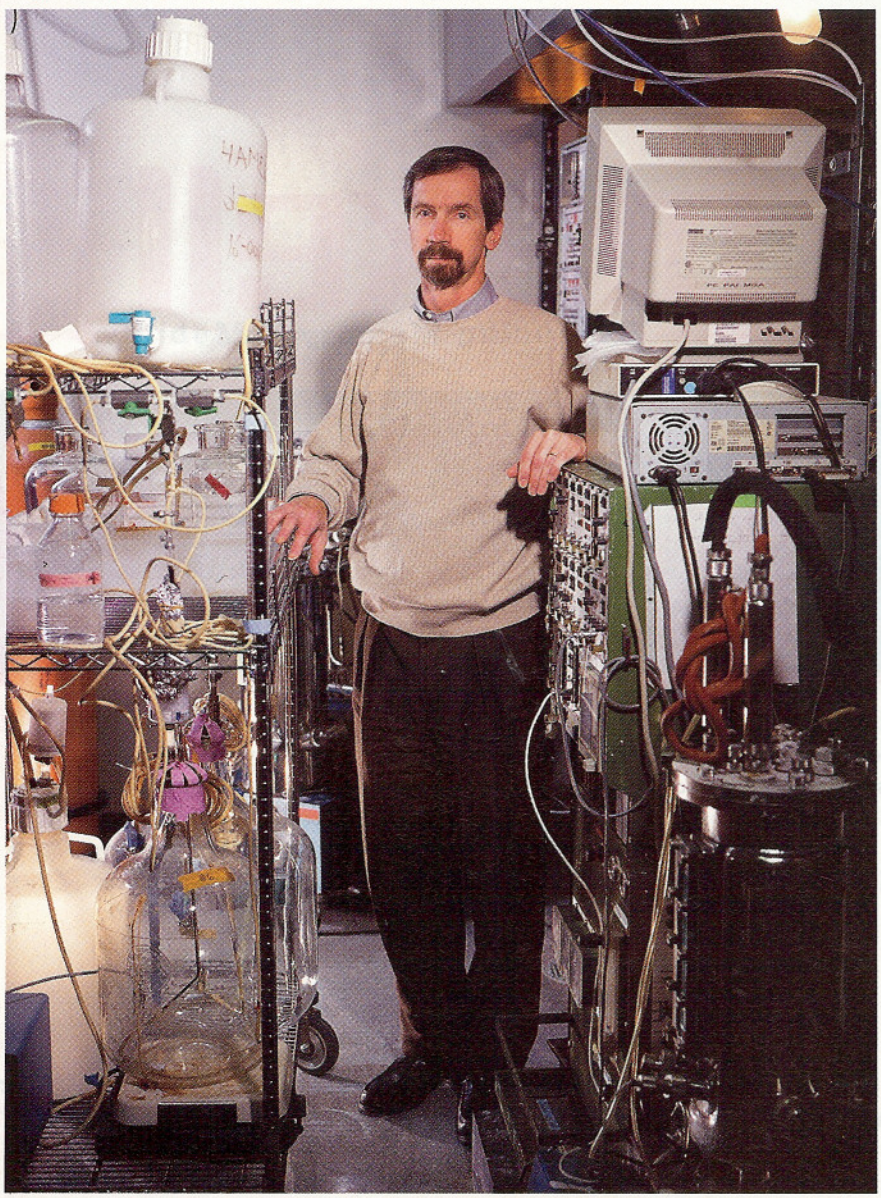
ously guarded, the new process involved breakthroughs in understanding the metabolism and physiology of the mouse cells so that scientists could give them what they needed to put out more protein. "With the old process we were producing about 700 to 800 milligrams of Synagis per liter of fluid in the bioreactors," says Young. "Now we've got it up to about three grams per liter, and we're making over four grams per liter in the lab."

Snarls in producing test quantities of Vitaxin, another drug in MedImmune's pipeline, led the company to adopt a product-development method known as design for manufacturability, or DFM. Companies that make consumer electronics gear, cars, and appliances already have the DFM religion. Their engineers are under orders to ensure that the parts they design are easy to manufacture and assemble on existing production lines.

Like the dim guitarist in *Spinal Tap*, biopharma people want to find the production-volume knob and crank it all the way up.

The problem with Vitaxin, a protein drug aimed at treating cancer and arthritis, was that persistent impurities were drastically reducing the yields. The cell culture used to produce Vitaxin was churning out two varieties of the molecule: a good one in reasonable quantities, plus small amounts of an inactive version that needed to be removed by purification. But the chromatography process used to separate the two types had trouble recognizing the bad molecules. MedImmune ended up having to toss more than half of the good molecules to ensure that the product met the FDA's purity requirements—the biochemistry equivalent of throwing out the baby with the bath water.

Bioprocess guru Charles Cooney of MIT sees big gains from innovations at the microscopic level.



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For help, MedImmune turned to Applied Molecular Evolution in San Diego, a biotech company that specializes in the "optimizing" of drug molecules. AME's method involves manipulating the segment of a microbe's DNA that directs the production of monoclonal antibody drugs—proteins that bind to and neutralize pathogens and their toxins. Like a musician playing variations on a theme, AME shuffles chemical rungs on the microbe's ladder-like DNA molecule to form a library of closely related variants. By inducing these variants to express, or produce, the proteins they encode, AME and its customers get a bunch of new molecules to test. With luck, one or more might prove to be better medicine than the original.

That's what happened with Vitaxin. "We were able to make changes at the site on the DNA that was causing some of the protein to degrade and become the bad variant," explains AME president William Huse, who runs the business with chief medical officer James Breitmeyer and CFO Lawrence Bloch. "Fixing that problem," continues Huse, "turned out to hurt the medical efficacy of the molecule somewhat, but we were able to make other changes at additional sites that brought back the efficacy plus more." The improved molecule looks like such a winner that MedImmune has scrapped its early-phase clinical trials of the original drug and is repeating them with the new version of Vitaxin. Meanwhile yields on the Vitaxin pilot-production line have tripled. "Optimizing new drug molecules with AME is an integral part of our upstream development now," says MedImmune's Young.

Cooney at MIT thinks disciplines like design for manufacturability will help biotech companies as much as they have other

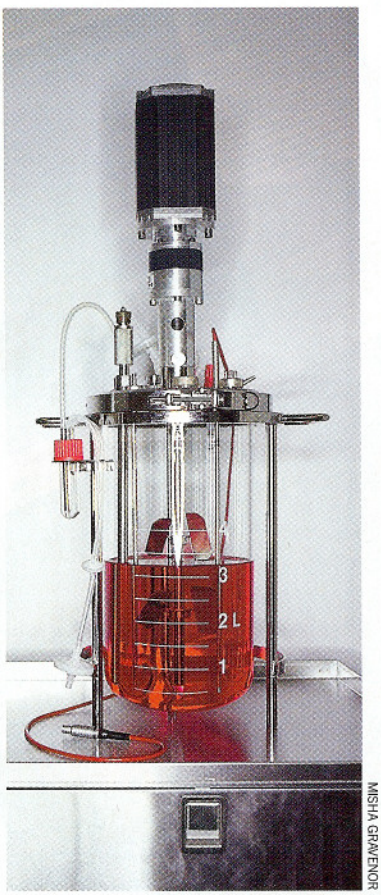
manufacturers. "If you think about this early enough in product development, it can offer big economic gains," he observes. "Purification is probably the most expensive and difficult part of the manufacturing process, so why not try to design drug molecules that have fewer impurities associated with them?"

In the rockumentary movie satire *Spinal Tap,* a dim guitarist has a special amplifier with a volume knob that goes to a maximum setting of not 10 but 11. That's what biopharma people want to do with their drugmaking cell cultures—find the production-volume knob and crank it all the way up. A company called Sangamo Biosciences in Richmond, Calif., has a method that promises to help. Sangamo specializes in engineering so-called zinc-finger proteins, which bind to the control region of a gene and can switch it on or off.

By stringing together several appropriate zinc fingers (the name relates to their molecular architecture), scientists can create a protein that recognizes and binds to any desired segment of DNA. That's no small feat; in human DNA it can mean finding a particular 18-rung section on a ladder that has three billion rungs. Sangamo's president, Edward Lanphier, compares his company's technology to the guidance system of a highly accurate missile. Once a drugmaker can pinpoint the regulatory region of a desired gene, it has found the volume knob and can pump up production by as much as 200%.

Sangamo is working with a number of biopharma firms that are looking to boost their yields. Medarex in Princeton, N.J., is now in clinical trials with several monoclonal antibody cancer drugs. Medarex makes its drugs in so-called transgenic mouse cells, which have human genes spliced into their DNA. "We're early in our collaboration with Sangamo, but we've got some glimpses of success," says Ronald Pepin, senior vice president for business development. "We hope this will help us get up to economic levels of expression faster or more consistently."

Creating a protein that can bind to human DNA means finding an 18-rung section on a ladder that has three billion rungs.



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Achieving consistent output in biopharma can sometimes be baffling. But it's a puzzle that can hold the clue to better yields for companies using fungal cultures to make drugs like antibiotics. Microbia in Cambridge, Mass., is applying its intimate knowledge of the complex regulatory and chemical-synthesis pathways inside fungal-culture cells to improve their medicinal output. Richard Bailey, the company's senior director of biomanufacturing business development, says helping a biopharma client improve production efficiency often starts with listening to the client's observations about unexpected fluctuations in the amount of good stuff the little critters in bioreactors are churning out.

"When a company brings us a cell that it wants to make more productive, the first thing we'll do is ask about transient conditions they've observed but don't understand," he says. For example, a drugmaker may notice that a change in the temperature or nutrient balance in a bioreactor results in a welcome but temporary increase in the cell culture's output, followed by a decline. "This tells us they've bumped into some regulatory mechanisms that they can't see," says Bailey.

Making more of itself is the prime directive nature has given a cell, which typically has about 150 internal metabolic pathways for moving raw materials around and carrying out the complex reactions that it needs to replicate. Think of this network as a railroad switching yard where a boxcar can be shunted onto one of many different tracks as it makes its way from one end of the yard to the other. The conventional method for hopping up the production of fungal cells has been mutagenesis, in which cells are exposed to chemicals or ultraviolet radiation to induce changes in their DNA, thus accelerating the trial-and-error process of evolution. Some of the resulting mutants may have better properties than the parent strain, and they become the new production workhorses. Scientists have increased penicillin production this way by about 15% a year for decades.

Microbia's innovation is to replace the randomness of mutagenesis with a mechanistic approach the company calls precision engineering. Working with gene chips—dense grids of molecular tweezers built to grip DNA—the company maps the structures of a cell's genes and the changes that have occurred in them over time, and determines which genes are switched on or off.

The genes that control production of the chemicals needed to synthesize a drug may number only a dozen, but first they must be found among the 4,000 genes in a humble *E. coli* cell or the 10,000-plus in a fungal cell. Then Microbia's scientists identify the best route through the cell's multiple metabolic pathways for assembling the proteins, toggling genes on or off to optimize productivity. Like the master of a railroad yard setting switches to clear the way for an express train, they can shut down other pathways that are draining energy from the desired reactions.

MIT's Cooney thinks biotechnology is entering a period in which scientists will be able to manipulate cells in increasingly profound ways. "We're just seeing the early examples now, and the number will increase dramatically," he predicts. What a welcome concept for the biopharma people: making more drugs without buying more hardware. F

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