the hit on the high-risk stock, and CoCensys forges ahead unscathed.

Some mature biotech companies are pursuing strategies similar to that of CoCensys. One is Genzyme Corp., based in Cambridge, Massachusetts, which earned $180 million last year, mostly from sales of Ceredase, an enzyme for treating Gaucher disease. In November 1990, Genzyme set up an affiliate company called Neozyme by selling "SWORDS" to public investors. SWORDS, an acronym for the ungainly "stock and warrant, off-balance sheet research and development financings," are stock options that allowed Neozyme investors to buy shares of Neozyme plus warrants to buy shares in Genzyme. Last year, Genzyme purchased four of its affiliate's six research programs, mostly on treatments for cystic fibrosis. "If Genzyme didn't buy back the program, it's a failure, and the return on the SWORDS would have been minimal," says David McLachlan, Genzyme's senior vice president for finance. But Neozyme did work, and its investors made money. As a result of that kind of success, "you'll see more of these kinds of ventures," predicts Oppenheimer's Casdin.

Only so many investors can be wooed back by creative stock deals, however, and that's where Congress may give the industry a boost. In February, bills were introduced in the House and Senate that would give a tax break to investors in small businesses, a category for which most biotech firms qualify. The bills would reduce the taxes levied on capital gains earned from investing in a company that raises up to $100 million for research and development. A similar bill passed Congress last year, but was vetoed by then-President George Bush when it was included as part of a Democrat-sponsored tax package. Congressional staffers expect the new bills to pass, if Congress and the Clinton Administration can agree on the amount of capital needed to qualify for the tax break. Congress and the biotech industry say $100 million; Clinton says $50 million.

The passage of a tax-break bill would give the biotech industry some relief, and creative financing strategies are helping companies pull through difficult times in the money markets. Nevertheless, it's still possible that the coming months could be a grim time for the industry, with many weaker companies going under as they fail to raise the money they need to bring their first profitable products to market. It's clear that the only thing that will offer long-term relief is the lifting of the dark clouds conjured by the talk of price controls. And that resolution can only come as the much larger questions of health care policy get sorted out. So, for the time being, the industry will have to rely on its boundless optimism and its ingenious financing devices to remain afloat.

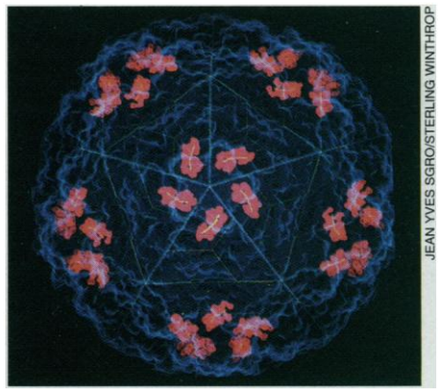
–Richard Stone

DRUG DEVELOPMENT

Going Back to the Future With Small Synthetic Compounds

For many years, synthetic chemists were the backbone of the pharmaceutical industry, creating many of the drugs that show up as the biggest profit-makers on the industry's balance sheets. Beginning in the 1970s, however, molecular biologists began to elbow the chemists aside. Armed with remarkable new recombinant DNA technologies, these upstarts were able to do something that had not previously been possible: Make large quantities of what had been extremely scarce—but potentially very clinically useful—human proteins. And the molecular biologists have been very successful, churning out a variety of proteins with therapeutic benefits and spawning the biotech industry along the way.

Within the past few years, however, both the larger drug companies and the smaller biotech firms have begun to go "back to the future" in an effort to replace those proteins with smaller, chemically synthesized molecules. Such compounds, which could be easier to take than proteins and might have fewer side effects, are currently being tailored to combat sepsis and its more severe complication, septic shock, which kills tens of thousand of patients annually, as well as diseases that range from the common cold to AIDS. But the list of potential targets is long, including diabetes and autoimmune conditions such as arthritis and psoriasis (also see Perspective by Joan Brugge).



JEAN YVES SGROI/STERLING WINTHROP

Virus blocker. By binding to receptor-docking sites, small molecules may prevent cold viruses from infecting cells.

While the work on this new generation of small molecules is at a very early stage—only a handful of drugs have gotten as far as clinical trials in humans—biotech researchers are pleased with the progress made so far. The idea of replacing proteins with smaller compounds "is about 5 years old, but it was thought it would take 10 years to get where we are now," says protein engineer Jim Wells of Genentech.

The motivation for this change of direction was the growing recognition that protein drugs aren't all that their makers hoped they would be. Not only are they tough to produce, even with the tools of biotechnology, they are even tougher to deliver—generally having to be given by injection (see p. 912). And contrary to the original expectation that these "natural" drugs would be more specific than anything the chemists came up with, many turned out to have multiple actions in the body and therefore to have side effects after all. "The opportunity for blockbuster drugs from recombinant proteins is very limited," says E. Fintan Walton, who's familiar with a wide range of biotechnology research because his firm, CONNECT Pharma Ltd. of Oxford, England, specializes in technology licensing and other business aspects of drug development.

But both problems might be eliminated with small, stable synthetic drugs designed to either mimic a protein's effects or to block them. Delivery would be easy, since such drugs could be taken in pill or capsule form. The unwanted side effects might disappear as well. Proteins can have multiple effects partly because they may work through two or more receptors, each of which brings about a different set of responses. If a small molecule could be designed to fit only one of those receptors, it ought to be more specific in its actions.

That double benefit of small drugs has drawn many companies into the field already. Among them is the gene-cloning pioneer, Genentech Inc. of South San Francisco. Indeed, the growing chemistry department at that preeminent biotech company is as good an indication as any that the tide is beginning to turn in favor of small molecule development. Several groups at Genentech are working to develop a small molecule substitute for human growth hormone (hGH), a protein hormone the company developed by recombinant DNA techniques, to stimulate growth in people who have a form of dwarfism. The hormone may also cause diabetes and unwanted lactation, however, and the goal of chemical synthesis, says Genentech's Tony Kossiakoff, "is to make a miniature, stable hGH" without side effects. A further incentive is also provided by the knowledge that the recombinant hormone will lose its protection as an orphan drug in March 1994.

The Genentech workers, like other researchers targeting their drugs at protein re-

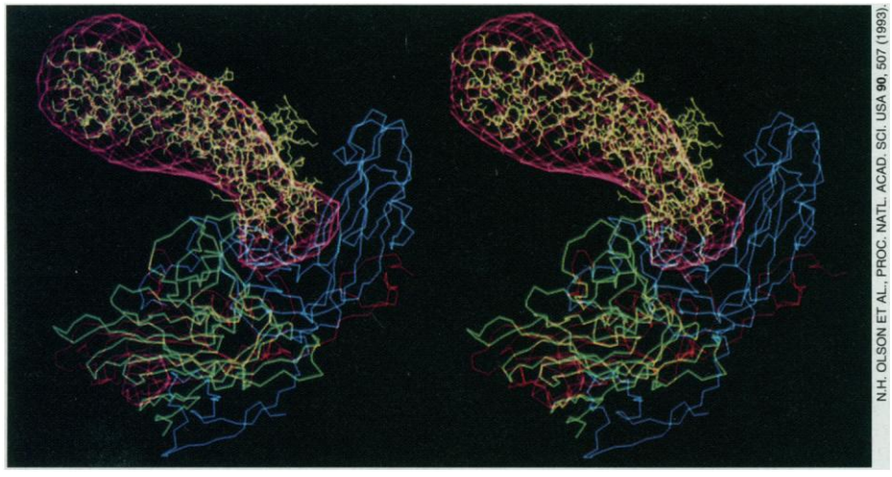
ceptors, are using the principles of rational drug design, essentially trying to design a drug from scratch. To do that, they first need to learn as much as possible about the structures of a protein and its receptor, and especially about how the two fit together, then they use the information to design a small molecule that can also interact with the receptor. However, in at least of couple of cases, including Genentech's hGH efforts, the structural information suggests that finding a small molecule to do the job could be problematical.

The Genentech work began about 5 years ago when protein engineers Wells and Brian Cunningham introduced a series of mutations into the hGH molecule as a way of identifying the amino acids needed for binding to the growth hormone receptor. Since those amino acids seemed to be grouped in two different regions of hGH, the work indicated that it might bind to two receptors, not just one. And indeed, early last year, crystallographer Kossiakoff, with Genentech colleagues Bart deVos and Mark Ultsch, confirmed that suspicion by determining the three-dimensional structure of hGH bound to the extracellular bit of its receptor.

Yet while the Genentech researchers were elated to have produced the first detailed look at a hormone-receptor complex, they realized that designing a small molecule that could mimic hGH's growth-stimulatory effects would be difficult. The problem is posed by the fact that one hGH molecule binds to two well-spaced receptors. As a result, Kossiakoff says, "the region straddling the two binding sites is large," making it hard to come up with a conventional small molecule that could span the gap as hGH does.

That didn't mean there is no solution, says Kossiakoff, since knowledge of the details of the hormone-receptor complex offered other strategies. The researchers found, for example, that when hGH binds to the outer regions of the two receptors, it pulls them together so that the parts near the membrane also come into contact. A small molecule might be able to bridge that smaller gap, bringing the receptor molecules together in an unnatural but effective way.

Though growth hormone occupies a secure market niche, that niche can't touch the market that researchers at Hoffmann-LaRoche Ltd., in Basel, Switzerland, have set their sights on. They're aiming to antagonize the action of the cytokine known as tumor necrosis factor (TNF). TNF contributes to development of arthritis and septic shock, a severe, even lethal, response to bacterial and other infections that afflicts about 125,000 people annually in the United States. Crystallographer David Banner, molecular biologist Werner Lesslauer, and their Hoffmann-LaRoche colleagues are using information from a crystallographic analysis of the complex between TNF and the extracellular domain of one of its two known receptors, the β receptor, to design new drugs that could counter septic shock.



N.H. OLSON ET AL., PROC. NATL. ACAD. SCI. USA 90, 507 (1993).

In the groove. The stereodiagram indicates how the rhinovirus receptor, an adhesion protein called ICAM-1 *(shown in red)* binds to surface proteins from a cold-causing rhinovirus.

The TNF molecule is a trimer, consisting of three identical protein subunits, and the Hoffmann-LaRoche group's analysis, which was published in the 7 May *Cell*, confirmed that it binds three receptors, with the receptor proteins poking into shallow grooves between the TNF subunits. Here the interface between the protein and its receptor is again large, however, and while the company has a TNF antagonist, it's a recombinant protein. Still, say Lesslauer, tests in animal models look promising, and the antagonist "will go into human clinical trials as soon as possible." Those trials will no doubt be monitored very closely by insiders in the industry, since disappointing clinical trials of a septic shock drug by three other biotech firms have contributed to the drying up of investment money that is now afflicting the biotech industry (also see p. 908).

While the sepsis market is substantial, the market for antiviral drugs, now in short supply, could be even more lucrative. And there, receptor studies, coupled with classic organic chemistry, have identified new—and small—antiviral candidates.

To enter and infect a cell, a virus must first bind to one of the cell's normal surface molecules, which becomes, in effect, a viral receptor. The idea is that if binding of the virus to its "receptor" could be blocked by a small, synthetic compound, it might be possible to prevent infection.

This strategy could ultimately be useful in treating many viral diseases, but the area that's currently moving ahead the fastest is the design of receptor-based therapies for dealing with the rhinoviruses that cause the common cold. That work has been aided by structural studies of both virus and receptor. In 1985 crystallographer Michael Rossmann and his colleagues at Purdue University produced the first, detailed look at a human rhinovirus. Just this year, Rossmann, Tim Baker, also of Purdue, and their colleagues followed up on the original work by using cryo-electron microscopy to provide a three-dimensional image showing how a whole, spherical rhinovirus binds to its cellular receptor, a cellular adhesion molecule known as ICAM.

Studies like those have revealed that human viruses can be prickly characters: polyhedrons with spikes and canyons. The studies also showed that viral receptors such as ICAM may bind to relatively small areas in the cavities at the bottom of the canyons. This information has been used by the drug industry as guides for designing small-molecule cold remedies. Sterling Winthrop Inc. of Rensselaer, New York, has identified two synthetic drugs called disoxaril and WIN 54954 that have molecular weights of about 300. Both bind to the pocket in the viral canyon of rhinoviruses and block attachment of most variants of the virus to ICAM, says company virologist Mark McKinlay.

"The opportunity for blockbuster drugs from recombinant proteins is very limited."
—E. Fintan Walton

Despite the high hopes for them, these compounds have been ineffective in clinical trials against common colds brought on by rhinovirus. But they have prevented a more serious type of cold caused by coxsackie virus, a related virus that also binds to ICAM. As a result, researchers are persevering in the work. "From our work and that of other companies, there's enough data to say this strategy has a good chance of working," McKinlay con-

cludes. The questions still to be addressed include whether cold viruses, which like other viruses have the chameleon-like ability to mutate, will evolve new tricks before the company can get its anticold compounds through lengthy trials and approval procedures. "It's a concern," McKinlay says, "but we remain optimistic."

Researchers have also been trying to block receptor binding by the AIDS virus, HIV, which latches on to a receptor molecule called CD4 on the surface of the T cells it infects. Original attempts to combat HIV infection with a soluble form of the CD4 receptor showed promise in tests on cultured cells but failed clinical trials. "It was a frustrating effort," says Ray Sweet of Smith Kline, Beecham, which made one of the compounds tested. Genentech dropped a similar effort.

Despite the frustrating results with soluble CD4, however, researchers haven't given up on finding a compound that can block HIV binding to cells. About 3 years ago, teams led by Howard Hughes Medical Institute researchers Stephen Harrison at Harvard and Wayne Hendrickson at Columbia performed x-ray crystallographic studies of a CD4 receptor fragment. Their results suggested CD4 makes contact with a viral glycoprotein resting in a groove on the HIV surface. The area of contact is about 25 Ångstroms by 12 Ångstroms, small enough that it might be possible to prevent binding with a small CD4 mimic that attaches to HIV, says Harrison.

Conversely, it might be possible to block the binding with small molecules targeted to CD4 itself. That approach could have an advantage, says James Jenson, a vice president at the startup firm Procept Inc. of Cambridge, Massachusetts, one of several companies looking for ways to block HIV binding to cells. He notes that existing AIDS drugs, such as AZT, target proteins associated with HIV, which mutate rapidly, making the virus drug-resistant. The human CD4 protein may be less subject to mutation and therefore a better target. Later this year, Procept plans to file an investigative new drug application with the Food and Drug Administration for one of its drugs, a small molecule custom-designed to block HIV binding to CD4.

Procept is only one of many drug companies where there's a pervasive new sense of looking back to forge the future. In that process, they're reinvigorating the venerable scientific specialty of synthetic chemistry. Synthetic chemists, who were once at the hub of drug development and whose contributions were recently spurned by a brash young generation of molecular biologists, are now regaining their stature as essential members of the drug development team. And molecular biologists are learning that synthesis is not just a way of producing drugs, but is also a collaborative means of doing top science.

–Anne Simon Moffat

DRUG DELIVERY

Stand and Deliver: Getting Peptide Drugs Into the Body

Beginning with recombinant human insulin, which went on the market in 1982, the biotech industry has produced a wide range of potentially life-saving new drugs. But in the pharmaceutical world, making a new drug is only half the battle. Once a drug has been developed, researchers face the challenge of figuring out how to get it into the body in doses high enough to do the job, but not so high as to poison healthy tissues and cells.

That's been a major hurdle for the biotech industry, since almost all of its products to date are large peptides or proteins. And proteins, because they are rapidly broken down by digestive enzymes and don't pass readily through the skin, can only be administered by costly, inconvenient, and painful injections. No wonder drug delivery is seen as a bottleneck by insiders like Russ Potts, director of research sciences at the biotech company Cygnus Therapeutic Systems in Redwood City, California: "Drug delivery represents the potential Achilles' heel of biotechnology's peptide drug industry."

The industry isn't backing down from the challenge. On the contrary, it is fighting to devise alternate methods for delivery of peptide and protein drugs. "Every major pharmaceutical company [has] at least an in-house pilot peptide drug delivery program; if not, they contract out to companies specializing in drug delivery," says Charlie White, director of marketing at Medisorb Technologies International, a Cincinnati-based company that performs such drug delivery research. Although it's too early to say when efforts to make peptide drugs available in noninjectable forms will pay off, Gordon Amidon, professor of pharmaceutics at the University of Michigan, Ann Arbor, says it's a good sign that "drug delivery has gained equal footing with drug discovery in the pharmaceutical world."

PHARMA-LOGIC INC.

Small world. Microcrystals of submicron size (the smallest here is 0.5 micron) might be used to deliver some peptide drugs.

Such "equal footing" is reflected by the enormous research activity now exploring several strategies for resolving the peptide delivery dilemma. Among them, three stand out as promising: Researchers are trying to develop body-friendly microspheres for oral delivery that will protect these fragile molecules en route to a desirable absorption site in the intestines; they are experimenting with ways to aerosolize them for inhalation and absorption through the lungs; and they are designing skin patches that use electric currents to drive proteins into the skin and the blood circulation.

Oral delivery: making peptides palatable

Oral delivery is a tantalizing double-edged sword for the biotech industry. On the one hand, it's the most desirable route for getting drugs into the body, because it's so convenient. Yet the oral route is also the most hazardous to the health of the peptides and proteins themselves, and probably will be the most difficult to achieve. In fact, "a decade ago oral peptide delivery was considered fantasy," notes pharmaceutical scientist Vincent Lee of the University of Southern California. And even today, though companies are plunging into the area, their early efforts have generated as much skepticism as excitement.

The problem is that proteins can't be taken in ordinary pills or capsules because their protective coatings break down in the stomach, exposing their contents to protein-splitting enzymes before they can be absorbed into the bloodstream. The trick, then, is to find a way to camouflage peptides and proteins long enough to slip them past the digestive enzymes to the intestinal lining, where chances for absorption are greatest.

Several companies think they can pull off that trick by protecting proteins from digestive enzymes by encapsulating them in microspheres—tiny particles, ranging in size from 50 nanometers up to 20 microns, made with any of a variety of inert materials, including synthetic and natural polymers. For example, InnoVet Inc., in West Palm Beach, Florida, working with Matrix Bioscience in Research Triangle Park, North Carolina, is experimenting with a natural fatty acid "biopolymer" to administer insulin orally; they say that they have had some success in rodents. Alkermes Inc., in Cambridge, Massachusetts, is using the corn protein zein to deliver its peptides. And, as offbeat entries, there are the "proteinoids,"