Biotech's Second Generation

This decade, scientists are out to design drugs that improve on nature, not just mimic it. And the diversity of their research approaches has bred optimism. But some say it's time to put up or shut up

After years of sustaining itself on an all-protein diet, the biotechnology industry is now trying to come up with a more balanced fare of genetically engineered drugs. Like adventurous chefs experimenting with new cuisines, white-coated scientists in the labs of biotech companies are cooking up novel drugs made with the other three major types of biologically active molecules—nucleic acids, sugars, and fats. The result is an eclectic menu of emerging drugs that could revolutionize medicine in the next decade.

"I think what you have is breathtaking research and product development that is the cutting edge of the pharmaceutical industry," says Harvey Berger, who left his post as president of research and development at Centocor Inc. last year to launch ARIAD Pharmaceuticals Inc. "It's producing the second generation of biotech products." And in one sense, some of this "breathtaking" research better pan out—because this decade could be the crucial one for the biotech industry's credibility. Wall Street has been bullish on biotech for a while, but the products haven't been winning approval at the Food and Drug Administration (FDA) in proportion to the rise in stock prices. As Thomas Cech, a University of Colorado biochemist on the advisory board of a new company called Ribozyme Pharmaceuticals Inc. (RPI), says about his ribozyme technology: "It has to happen this decade or the investors will pull out."

What are the approaches that researchers like Cech are betting their companies on? These technologies are a far cry from the first generation of biotech products, which were largely genetically engineered proteins that worked more or less like their natural counterparts, such as recombinant versions of human insulin and growth hormone. Today, researchers are not just looking to reproduce the activity of natural molecules, they're trying to improve on nature. "We're taking processes we learned from nature, but now we're redirecting them in a completely different way," says Cech.

In their search for this decade's winning biotech products, researchers are pursuing a number of quite different approaches:

- Some are focusing on the genetic code, trying to design drugs that block it from spelling out the instructions for making disease-causing proteins, such as those specified by the cancer-causing oncogenes or those that cause cystic fibrosis and other inherited disorders.
- Others are using novel classes of molecules, such as carbohydrates, or making their own custom peptides and small organic molecules to block receptors on the outside of cells. Once in place, they can ward off viruses or white blood cells that cause inflammation or other harmful immune responses.
- A few are designing small organic molecules or harnessing lipids to interfere with the signaling pathways inside the cell that lead to the uncontrolled growth of cancer, or to inflammation, cystic fibrosis, and other diseases.

Which of these technologies is actually going to wind up curing patients? It's still much too early to say—although Wall Street keeps trying to guess. "All of these technologies are very much exciting at this stage of their evolution," says George Poste, chairman of research and development at SmithKline Beecham. "So, it's very difficult to say what's going to make it to the clinic and what isn't." In the absence of a crystal ball, the best *Science* can offer is a tour of some of the most promising research—with the knowledge that "some will succeed and some will fail," says Berger.

Code blockers

In many cases there are good reasons to block disease-causing genes from making the proteins they specify. One way is to block protein synthesis at its very first stage—the transcription of DNA into messenger RNA. "The best target is the hub of the wheel," or the DNA at the nucleus of the cell, says Carnegie Institution molecular biologist Steven McKnight, an expert on the proteins, known as transcription factors, that turn genes on and off.

Indeed, McKnight is so confident that transcription is the place to intervene in protein synthesis that along with Robert Tjian of the University of California, Berkeley, and David Goeddel of Genentech, McKnight is helping to launch Tularik Inc., the first biotech firm to focus solely on developing drugs that work by either blocking or mimicking transcription factor action, depending on the effect desired (*Science*, 20 March, p. 1506). McKnight is planning to leave Carnegie in August, but even before he arrives at Tularik's south San Francisco lab, half a dozen researchers are screening chemicals to see if they can find any that selectively block specific transcription factors without inhibiting those that are essential to keep the cell alive.

Their first target will be viruses, such as herpes, that sneak into the cell armed with their own transcription factors that turn on the cell's genetic machinery so that the virus can reproduce itself. The researchers hope to prevent

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the virus from reproducing by sending in chemicals that specifically block the viral transcription factors, without inhibiting normal cell activities. Once they are confident that they can block transcription factors selectively, the researchers hope to find drugs that inhibit the transcription factors that turn on genes causing cancer, heart disease, and inflammation. Or, alternately, since researchers have identified several genes that can suppress tumor cell growth, as well as those that stimulate it, they might look for ways to turn on these suppressor genes as a way of preventing or treating cancer.

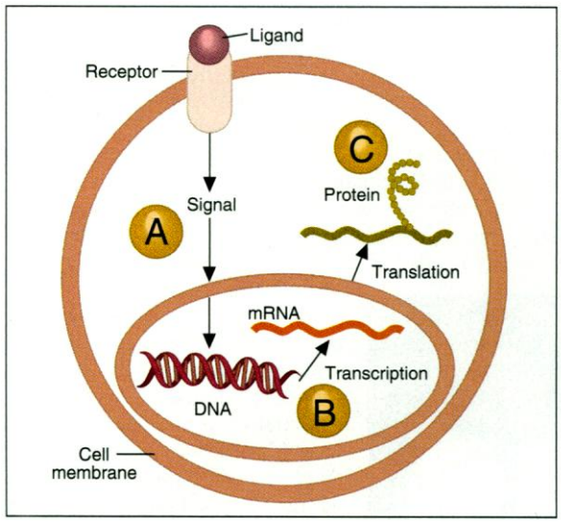

ILLUSTRATION: J. CHERRY

Target practice. New biotech drugs take aim at the various cellular starting points of disease: **(A)** signal transduction, **(B)** gene transcription, and **(C)** protein synthesis.

Making antisense

Other researchers, however, prefer to block protein synthesis at the next step, after the messenger RNA is made. The most widely known—and hyped—of these approaches is called the "antisense" method, in which researchers design antisense oligonucleotides, short pieces of nucleic acid that recognize and bind to specific messenger RNAs. In theory, the two stay bound long enough to prevent the messenger RNA from producing a protein. In practice, however, it is difficult to deliver adequate concentrations of oligonucleotides into the cell and keep them bound to the messenger RNA long enough to inhibit protein synthesis significantly.

Nevertheless, several firms say they are on the verge of overcoming such difficulties. ISIS Pharmaceuticals near San Diego has begun clinical trials of an antisense oligonucleotide designed to inhibit the growth of papillomavirus, which causes genital warts, a condition that is both painful and a risk factor for genital cancers. "It's the first oligonucleotide to be administered to human beings," boasts pharmacologist Stanley T. Crooke, chairman of ISIS, who hopes to win approval later this year from the FDA for clinical trials of another antisense drug to treat herpes.

Down the Pacific Coast Highway from ISIS, San Diego's Genta Inc. has initiated human trials to test an antisense drug to help fight leukemia. In these trials, antisense drugs are used in tissue culture to bind with leukemic cells in bone marrow that has been removed from patients who are to undergo massive, bone marrow-destroying chemotherapy. Afterward, the treated marrow will be transplanted back into patients to restore their immune systems. Despite initial skepticism about antisense oligonucleotides, Crooke says "half of the world's big pharmaceutical companies have flipped over and decided to get interested in antisense."

Drug companies also are taking a good look at what may be an even more precise way to block protein synthesis: using bits of catalytic RNA (called ribozymes) that work like molecular scissors to snip a messenger RNA that holds the code for building a disease-causing protein. This technology comes out of the Nobel Prize–winning work of Colorado's Cech and Sidney Altman of Yale University, both of whom have since helped start new biotech companies. Altman joined the scientific advisory board of Innovir Laboratories in Manhattan in 1989, while Cech agreed in February to serve on the scientific board of RPI Inc., which is about to move its headquarters to Boulder.

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–Harvey Berger

While the companies use different methods to cleave RNA, both are planning to use the technology first to cut the RNA of viruses that infect humans. Because of the highly competitive nature of the work, company spokesmen declined to specify which viruses, however. Once the companies' researchers have demonstrated adequate precision with viruses in human trials, they hope to use the shears to cut out the RNA holding the code for proteins that cause certain cancers and genetic disorders. At Innovir, researchers already have been able to "show that we can cleave very, very precisely," says Innovir chairman Allan R. Goldberg, a biochemist at Rockefeller University. That has given them confidence to design oligonucleotides that act like markers on a piece of messenger RNA to guide a natural enzyme, called RNase P, to cleave the target RNA, including that of human leukemic cells in culture. But Cech warns that it may take a while to develop drugs for culture: "This is technology that's proven to work under very artificial conditions in the laboratory, but certainly not proven to work in whole animals, so there's really quite a bit of research before we're ready for animal and human trials."

Block that receptor

Other biotech laboratories are finding targets for their new drugs not in the genetic material inside the cell but in the many receptors located on the outer cell surface. The idea is to send in a chemical that binds with a receptor, much as a spaceship docks with a space station, and thereby prevents the binding of molecules that would normally interact with the receptor and initiate cellular responses. While many existing drugs work this way, there is a new sophistication in the design and discovery of the next generation of receptor binding drugs.

Some biotech companies are using state-of-the-art computing tools to design small organic molecules that bind with receptors with exquisite precision, while other researchers are using peptides and new classes of molecules, such as carbohydrates, to block receptors. Others, such as Chiron Corp., Selectides, and Affymax, are becoming skilled at screening tens of thousands of these synthesized peptides to find the ones that work best. These new technologies are particularly promising for treating immune disorders, such as rheumatoid arthritis and multiple sclerosis, and for preventing the immune responses that cause inflammation and organ transplant rejection.

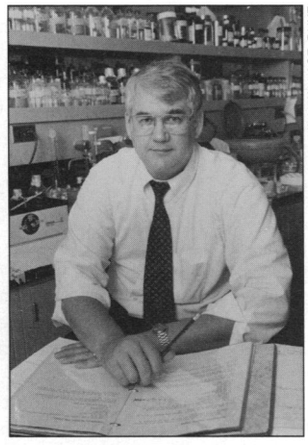
Take, for example, Glycomed Inc. in Alameda, California, which is trying to use sugar-containing carbohydrates to block the influx of white blood cells that cause inflammation. The cells get into tissue by adhering to receptors on the endothelial cells lining the blood vessels, and the Glycomed researchers have designed a carbohydrate that binds to those receptors—in effect sugar-coating the outside of the endothelial cell so that white blood cells won't stick to it. So far, it is working well in animal trials, and the company hopes to test it in humans next year, says Glycomed vice president for research and development Neil Ackerman. The carbohydrate-based drug may have an advantage over early protein drugs, because it may be possible to take it in a pill. But in other ways, the proteins have an advantage, because it's much harder to control the structure of complex carbohydrates during large-scale manufacture.

Not so insipid lipids

Another major class of molecules that is getting more attention from the biotech industry lately is the fats or lipids. Lipids had been

neglected, says biochemist Robert Bell, who is head of the Duke University Medical Center's section on cell growth, regulation, and oncogenesis, because researchers didn't fully appreciate their importance. But, he says, "these so-called insipid lipids play an incredibly complex role in life's processes."

Like carbohydrates, lipids have many roles. As the molecules that form cell membranes, lipids help control the movement of materials in and out of the cell. But it wasn't until the early 1980s that Yasutomi Nishizuka of Kobe University in Japan and Bell and his colleagues at Duke discovered that lipids also have a more dynamic role. When certain growth factors activate cell receptors, for example, they cause the release of a lipid—diacylglycerol (DAG)—that acts like a switch to activate events inside the cell. It does this by turning on a powerful enzyme called protein kinase C (PKC), which helps regulate cell growth and maturation. When PKC is over-active, it can lead to the uncontrolled cell division that causes tumors.



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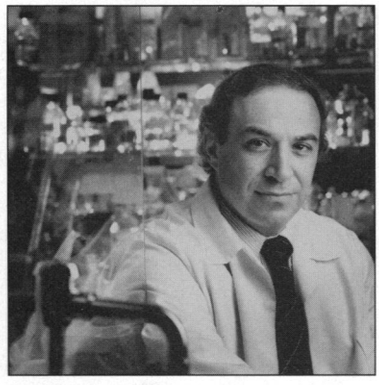

ROBERT REICHERT

Biotech chefs. Robert Bell *(top)* is turning fats into drugs while Allan Goldberg is using ribozymes.

As soon as these new roles were described for lipids, Bell tried to interest the major drug companies in his research, "but I was clearly too early." So, in 1987 he joined one of his postdoctoral researchers, Carson Loomis, in founding Sphinx Pharmaceuticals Corp. in Durham. Today, he has a collaboration with Eli Lilly Co. to promote the development of lipid regulators of PKC—and his list of potential disease targets includes cancer, cardiovascular diseases, psoriasis, and arthritis. The company is also testing a drug called Kynac, a synthetic form of a lipid known as a sphingosine, which appears to inhibit DAG from activating PKC, thereby keeping PKC in check.

Intracellular messengers

While Sphinx is the only startup focusing entirely on lipids to try to influence the way signals are transmitted inside cells (an area known as signal transduction), other new companies are also beginning to develop drugs that work through intracellular signaling pathways. Berger's new startup, ARIAD, has brought together a number of star chemists and cell biologists to design drugs that can be given orally to alter communications inside the cell selectively. Rockefeller University biologist and Nobel Prize–winner David Baltimore is the most visible of the scientists on the company's scientific advisory board, but it also includes Harvard University's Stuart Schreiber and Memorial Sloan-Kettering's James Rothman. Molecular biologist Joan Brugge, a recognized expert in signal transduction, also will leave her post at the University of Pennsylvania this month to become scientific director of the company.

The company's strategy is to design small organic molecules that block interactions between protein components of signal transduction pathways. One such target, for example, is a G-protein inside white blood cell membranes that responds to stimuli telling the cells to migrate toward a site where there is inflammation. The hope is that blocking the G-protein activity will inhibit inflammatory responses. ARIAD is also working on drugs for restoring the ability of mutant cystic fibrosis proteins to usher chloride ions out of the cells.

Such work to design small molecules that influence intracellular signaling events clearly is at the frontier of biotechnology research. But as observers such as Poste at SmithKline Beecham warn, it will take years, if not decades, before much of this cutting-edge research produces drugs. He says: "Our capacities in molecular biology have far outstripped our capacity in producing pharmaceuticals. The most challenging question is how far the fundamental issues are being addressed, with regard to technical feasibility, cost, and drug delivery."

The scientists at these startups, though, say those questions are foremost on their minds. Even though they may be in the earliest stages of R&D, they have a powerful incentive to turn their R into D—their companies' survival. Partly for that reason, most of the companies are now trying to develop several kinds of drugs aimed at different diseases, whether or not they are made with the same technology. "What's going to hit big time, isn't clear," says Massachusetts Institute of Technology biologist Phillip A. Sharp. "But there's a continuous stream of things coming out, aimed at major diseases. Hopefully we'll have an impact on them."

–Ann Gibbons

STATE POLICY

Massachusetts Woos Biotech Investment

While the biotech industry has begun to bring its first few products to market, right now it's bigger on ideas than sales. But Wall Street investors aren't the only ones betting that those ideas will pay off in the long run. Many states have pinpointed biotech's potential growth as a much-needed economic shot in the arm—and are actively courting those companies in hopes of attracting biotechnology investment. Take, for example, Massachusetts.

The state has long had an embryonic biotech industry. Indeed, it was only natural that firms such as Biogen and Genzyme would set up shop there, as commercial outgrowths of the molecular biology research being carried on at Harvard, the Massachusetts Institute of Technology, Tufts, and the state's hospitals and medical schools. But for a long time, the still nascent industry's potential for growth was overshadowed by the state's giant high-tech computer and electronics industries. Now those industries are in decline, and Massachusetts officials are like ardent suitors in their efforts both to woo new biotech firms and to keep the ones the state already has. They especially want to encourage firms that are beginning to move out of a strictly research mode to build their manufacturing plants in the state as a potent source of new jobs. "We're playing offense. If someone is thinking of expanding, we're knocking at the door to ask how we can help them," says Stephen Tocco, the state's secretary of economic affairs.

Official help. Acting on recommendations made last summer by a biotech task force of industry executives, Governor William Weld, Tocco, and others in the administration have agreed to lobby the Massachusetts legislature for economic reforms needed to make the state more fiscally stable and business friendly. They also plan to streamline the regulatory process needed for new plant approval and set up educational programs to provide a trained work force for the new manufacturing concerns. At the same time, many local municipalities, Boston foremost among them, are chipping in with their own programs to foster biotechnology.

And there's no denying that the efforts are needed if the state wants to rebuild its industrial base. Between 1988 and 1991, some 300,000 Massachusetts workers lost their jobs, 40,000 of those from high-tech industries, including the computer and electronics industries. Anticipated cuts in Pentagon funding for defense research and manufacturing