ego may have come across another promising candidate in the leumedins, compounds that prevent neutrophils from displaying the Mac-1 integrin on their surface.

Sticking it to the common cold

While it's easy enough to believe that adhesion-molecule research will pay off in wound-healing and inflammation, it's not so easy to imagine it fighting the common cold. But it is. In 1989, researchers discovered that the human rhinoviruses, which cause about 50% of colds, enter the body's cells by latching on to the adhesion molecule ICAM-1. Companies like Molecular Therapeutics and Boehringer Ingelheim rushed to exploit this new knowledge and have shown, in test tubes, that soluble ICAM-1, acting as a molecular decoy, can block infection of cells. And while many of those companies are still pursuing soluble ICAM, some doubts have cropped up. "It was a fascinating discovery, but it hasn't panned out because soluble ICAM just isn't very sticky," contends Upjohn's Anderson, explaining that the concentrations of the molecule needed to show an effect were too high for medical use.

"It's hard to find anyone, including the large drug companies, that doesn't have an effort...."

—Dale Cumming

Those suffering from the sniffles need not give up hope, because research in the area is continuing. In the June issue of *The Journal of Virology*, leading cell adhesion researcher Timothy Springer of Harvard Medical School, who will chair Leukon's science advisory board, and colleagues report on a promising alternative to soluble ICAM. They have created a type of molecule called an "immunoadhesion" by using genetic engineering techniques to fuse antibody fragments to the rhinovirus-binding portions of ICAM-1.

These constructs have a dramatically improved ability to bind to rhinovirus, says Springer. One immunoadhesion, for instance, was 200 times more effective in the test tube than ICAM-1 at blocking infection by cold viruses. While a cold is more nuisance than dangerous infection, such work could lay the foundation for blocking other, lethal viruses that might also invade cells via adhesion molecules.

Why cancer cells roam

Even further afield, and perhaps more speculative, the growing understanding of cell adhesion may open up another front in the war on cancer. The link between cell adhesion and cancer lies in metastasis, in which cancerous cells separate from a primary tumor and disperse throughout the body to sprout new tumors—with deadly results. The adhesion molecules displayed by metastatic cancer cells are very different from the complement found on normal cells, or even on nonmetastatic cancer cells, notes Richard Hynes, director of MIT's Center for Cancer Research, and the changes may permit these roving cells to escape from a primary tumor and then move through the bloodstream to seed new tumors. If researchers could understand these adhesion changes they could perhaps prevent them—thereby preventing the cancerous cells from dispersing.

Some clues to how that might be done are coming from two groups of German researchers at Heidelberg's Cancer Research Center and Karlsruhe's Nuclear Energy Research Center. Last summer they reported that the adhesion molecule CD44, found normally on lymphocytes, also studs the surface of pancreatic tumor cells that are metastatic. They hypothesize that the CD44 disguises the cancer cells as white blood cells and allows them to circulate freely in the bloodstream (*Science*, 31 July 1992, p. 614). Metastasizing cells from other cancers may hitch a ride on platelets, by binding to their P-selectin, and again evade the immune system's detection.

The research on adhesion molecules' roles in cancer, while in its early stages, does suggest some medical uses. There is the potential for new diagnostic tools, assuming researchers can accurately correlate levels of certain adhesion molecules with how invasive a tumor might be. Or, as a temporary treatment, "you could envision giving an anti-adhesion agent during the surgical removal of a primary tumor," says Cytel's Jim Paulson. That could increase the chances that the immune system would destroy any cancer cells shed into the bloodstream because of the operation.

The work on cancer may be in the early stages, but the same cannot be said of cell-adhesion work overall, which is in full swing. Indeed, researchers believe that most of the major cell-adhesion molecules have already been identified, and they now face the task of determining which ones are crucial for specific diseases and how their deleterious sticking—or failure to stick—can be manipulated. There most certainly will be a mad dash from biotech and drug companies to get products into clinical trials and through FDA approval, a process that, if history is any indication, will weed out a tremendous number of experimental treatments. For the moment, however, optimism reigns. Says MIT's Hynes: "The field is very exciting, the science is rolling quickly, and the biotech applications add extra spice."

–John Travis

INDUSTRY FINANCE

Biotech Sails Into Heavy Financial Seas

If biotech executives are beginning to have something of a sinking feeling, they have good reason. Aside from a temporary surge last fall, biotech stocks have been declining since January 1992. In the past 4 months alone they've dropped 40%—bringing the total loss to 50% overall. Investors are shying away partly because of the unease created after three highly touted sepsis drugs failed to perform up to Wall Street's expectations in clinical trials (*Science*, 26 February, p. 1243).

But the antiseptic backlash isn't the only problem for the industry. In March, President Bill Clinton, unhappy with the rising cost of prescription drugs, began floating the idea of price controls as a possible fix. Clinton's tough talk instilled fear among investors, many of whom are cashing in their biotech stocks in case the president follows through on his "hints." "You can see the kind of impact just talk of price controls has had on the biotechnology industry," says G. Kirk Raab, president and chief executive officer of Genentech Inc.

At the heart of the apprehension generated by price controls is one fear: If controls were in place, a biotech company would be unable to shower its investors with profits from a blockbuster new drug. "Price controls on new drugs have the potential of killing the industry," says the downbeat Raab. The reason is that while biotech firms have lots of promising new drugs in the pipeline, they don't have many products on the market. Therefore, they have to tap investors constantly to keep their books balanced. And if the investors constantly see returns that—due to price controls—seem minuscule compared to what they're used to, they're going to look elsewhere for their profits.

In foreign hands?

To some industry analysts, this scenario may wind up putting some of the United States' best biotech research in the hands of foreign owners, much as Japan ended up controlling the semiconductor industry in the late 1970s. "This is a watershed year," says venture capitalist Robert McNeil, general partner of Sanderling Ventures, which counts nine biotech companies in its stable. McNeil plans a business trip to Japan in June 1994. If price controls are enacted, he says he'll be there to sell off companies, rather than to forge collaborations with Japanese firms.

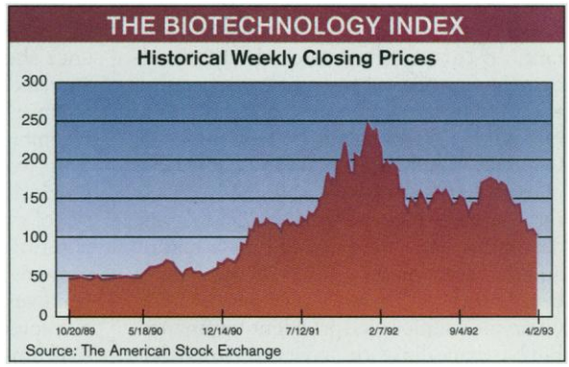
In past years, scientists and businessmen

had little problem snaring seed money—$500,000 to several million dollars—to launch a small biotech company and explore a hot idea. But recently, many venture capital firms have battened down their hatches to await Clinton's decision on price controls. Take the Massachusetts-based Oxford Bioscience Partners, which from September 1992 to February 1993 helped launch four new companies. "We're pausing to catch our breath and see what the implications of Clinton's policies are," says Oxford's Alan Walton, who served as a science adviser to President Jimmy Carter. It's not that there isn't plenty of venture capital out there, says Walton. He estimates that since 1987 about $300 million a year has been sunk into biotech firms, mostly startups. But much of this year's war chest is under lock and key until the price-control bugaboo goes away. Venture capital "is going to come to the industry in bite-sized portions," predicts Jeffrey Casdin, an analyst at Oppenheimer & Co. in New York City.

And it's not just the fledglings that are having trouble raising money. Established biotech firms are experiencing problems, too. The typical company needs about $300 million to develop a drug, says Lisa Raines, vice president for government relations at the Industrial Biotechnology Association. The first step toward getting that kind of money is usually selling shares of stock to public investors (individuals as well as pension and mutual funds), who account for about half the money invested in the biotech industry. From July 1991 to June 1992, 47 biotech firms made their "initial public offerings," netting $1.4 billion, or $30 million each. But this year, "the public market is sputtering at best," says Kenneth Lee, an analyst with San Francisco-based Ernst & Young.

Backing his opinion are bleak numbers: In February and March, biotech companies looking to make the jump from private to public enterprise raised a total of $17 million, compared to $200 million in January, just weeks before the latest sepsis news and Clinton's views on health care hit the newsstands. If we tried to raise money right now, it would be "impossible," agrees George Rathman, chief executive officer of Bethell, Washington-based ICOS Corp. Rathman's firm has enough money in the bank—$96 million—to wait for a change in the investment climate.

But other companies that have fewer cash reserves and have to refinance in the next 6 months "have plenty of reason to worry," says James Cavanaugh, a venture capitalist whose firm, HealthCare Investment Corp. of Edison, New Jersey, has helped launch 37 biotech companies. If Clinton doesn't make the talk of price controls go away soon, "a lot of small biotech companies could go out of business," predicts Rathman.



Roller-coaster ride. After climbing steadily, the value of 15 leading biotech stocks has been declining for 15 months.

Divining hidden sources of money

Although the current financial weather is mostly overcast, biotech firms are perfectly capable of getting out their umbrellas—or inventing new ones. In the past, the industry has proved very skillful at finding clever ways to finance what they want to do. "The biotech industry has created more innovative ways to finance [itself] than any other industry," claims Cynthia Robbins-Roth, editor of the monthly magazine *BioVenture View* and formerly a business manager with California Biotechnology Inc.

San Diego-based Ligand Pharmaceuticals Inc. recently exploited one of those innovative methods. The company is screening for drugs that might be used to treat any of several common diseases, including cancer, heart disease, and osteoporosis. But even though Ligand's potential markets are very lucrative, last fall, when company officials were ready to go public, they knew they would have a tough sell.

So last November, Ligand unveiled a strategy that was designed to calm the nerves of skittish investors. With every regular Ligand share investors bought, they received a "warrant" share. If the regular shares fail to rise in value 20% within 2 years, the warrants will convert to regular shares. That way, says Lee of Ernst & Young, the investor gets "a bigger piece of a smaller pie."

Irvine-based CoCensys Inc., which is developing a family of potential epilepsy drugs called epalons, is taking another tack in the brave new world of biotech finance. CoCensys wanted to test research ideas outside its main lines of work, including glycine substances to mitigate stroke-induced brain damage. The company was fortunate enough to have $40 million in cash reserves, but most of that money is earmarked for research on epalons. Instead of risking its reserves on less advanced projects, last October CoCensys set up an independent company called Acea Pharmaceuticals Inc. to study the glycine antagonists. By touting its solid reputation in the investment community, CoCensys was able to raise enough venture capital to get Acea going. If a particular compound developed by Acea pans out, CoCensys will license it and Acea investors could make a killing. If not, Acea's investors take

WHERE BIOTECH COMPANIES GET THEIR MONEY

They can:	Amount available in 1992 (millions $)	Percentage of Biotech funds *	Who does it?
Sell shares of stock	3200	48	Young firms that need money for preclinical testing of drugs Mature firms that have products on the market
Sell a product	2000	30	A handful of firms, because only a few biotech products have won FDA approval so far
Enter a collaboration with a pharmaceutical or biotech company	1000	15	Firms of all ages might sell the rights to market potential drugs to raise cash
Raise venture capital	300	3	New firms that need "seed" money to explore a research idea Young firms that require cash to finance preclinical testing of promising drugs
Enter a collaboration with the government	100	1.5	Occasionally, the U.S. government will pay firms to conduct research

*Other sources account for about 3% of biotech funding.

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 SGRO/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-