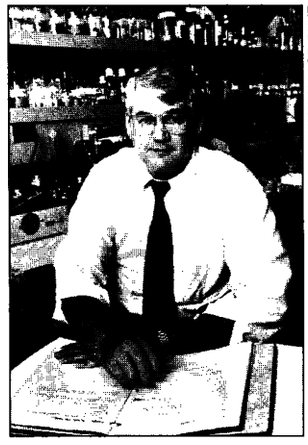
neglected, says biochemist Robert Bell, who is head of the Duke University Medical Center's section on cell growth, regulation, and oncogenesis, because researchers didn't fully appreciate their importance. But, he says, "these so-called insipid lipids play an incredibly complex role in life's processes."

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.



JIM WALLACE, DUKE

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

in Massachusetts are expected to cost another 30,000 jobs.

But if the state can hold on to the biotech manufacturing plants, 70,000 new jobs will be created in the industry over the next decade, Tocco says. And while it's too early to tell how well Massachusetts' efforts will do in the long run, state officials can point to at least one sign of success. Genzyme Co. had seriously considered building its new $75 million manufacturing plant in another state, but last March the company, thanks partly to Weld's direct intervention, broke ground for the plant in the Allston section of Boston.

Budget backdrop. Much of the state's push to aid the biotech industry has been directed at reversing its reputation for being "antibusiness," a reputation industry experts say was earned when Michael Dukakis was governor. Peter Feinstein, president of Feinstein Partners Inc., Cambridge-based consultants to the biotech industry, recalls Massachusetts in those years as a place that squeezed both its businesses and citizens for tax revenues, earning it the nickname "Taxachusetts."

What's more, the high taxes were accompanied by a riches-to-rags scenario that had the state topping national statistics for employment and growth one moment—the so-called Massachusetts miracle—and in the next moment garnering the second lowest bond rating in the country, just ahead of Louisiana's. The state's economy was in such disarray, says Marc Goldberg, president and CEO of the Massachusetts Biotechnology Research Institute, that doing business there had become "like operating in a Third World nation."

Indeed, the dismal state of the Massachusetts economy helped Republican Weld gain office in 1990 in the traditionally liberal and Democratic state. One of his vows was to improve the state's business climate. And he began by reaching out to the new growth industries, biotech among them. He asked Henri Termeer, president of Genzyme, to set up a task force of industry experts and executives to see what biotech needed.

The task force came up with two major recommendations. First they wanted a stable economy and a refined tax structure. Biotechnology manufacturing plants are a lot more sensitive to fiscal instability than most other manufacturing concerns, says Garen Bohlin, executive vice president of the Genetics Institute and current president of the Massachusetts Biotechnology Council. "Each site has to get FDA [Food and Drug Administration] approval, and reams of data have to be submitted on the process itself. Manufacturing decisions have to be made very far in advance. When faced with those decisions, the biotech executive has to have a warm feeling about the fiscal responsiveness of the state."

And just as important, the task force also wants Massachusetts to streamline its regulatory process as many other states have done. In some of them, all the necessary permits can even be obtained from a single centralized agency. But before a biotech plant can be up and running in Massachusetts, says David McLachlan, senior vice president of finance at Genzyme, a company might have to obtain between 20 and 30 different permits from different state and city agencies, in addition to the FDA.

Task force members say that Weld appeared responsive when they presented their recommendations to him last August. And just 2 months later, when Genzyme announced its intentions to put up a $75 million production plant for manufacturing thyroid stimulating hormone and an enzyme used to treat Gaucher disease, they got to see just how responsive.

Within a week of the announcement, says McLachlan, Weld showed up in the Genzyme corporate offices in Cambridge and "showed a real interest in keeping us," he says. At the same time, other states showed a real interest in luring Genzyme's plant away. Some states promised lower taxes, some had less red tape. But following an exhaustive search, Genzyme narrowed its choices to 12 states, including all of New England, Minnesota, Illinois, North Carolina, California, and New Jersey, plus Puerto Rico.

In the end, it was the governor's written assurances that convinced Genzyme to build its new plant in Allston just across the Charles River from its headquarters in Cambridge, says McLachlan. Weld promised to recommend legislative and administrative changes to make the state more favorable to business. The state has agreed to provide a tax incentive package that maintains corporate income taxes at current levels, expand tax credits already in effect for research, and assist firms in gaining predictable local property taxes. The state is also trying to reduce the capital gains tax. In addition, the state has agreed to expedite the permitting process and to provide a liaison for all contact with state agencies. "It should be that way for everybody," says McLachlan. And it will be, says Tocco, who emphasizes that the agreement was not "Genzyme-specific."

Boston helps out. Massachusetts has a few more tricks up its sleeve. Tocco reports that the state is considering installing a rapid-transit line to link the burgeoning biotech community in Worcester, an hour's drive from Boston, with the Boston/Cambridge biotech community. And, he says, they are trying to convince the FDA to locate a branch office in Boston focused on biomedical review.

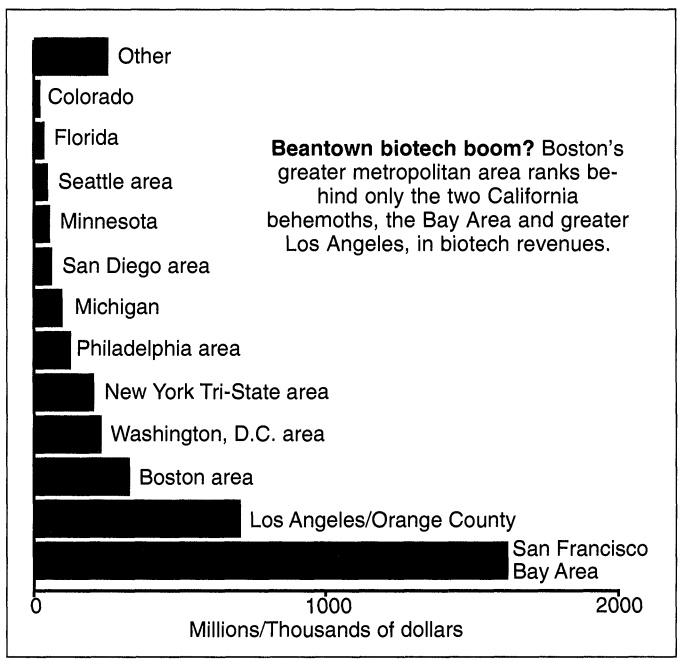
Municipal governments—in particular Boston's—are also aiding the state in the race to attract and keep the biotech companies. Last summer, the city's transportation commission announced that it was considering several plans for a biotech mass-transit line, a spur of which will stop at the new Genzyme facility in its slightly out-of-the-way locale.

And the Boston Redevelopment Authority (BRA) is planning new sites for biotech and bringing companies together with potential landlords, says BRA assistant director Gerald Kavanaugh. In fact, former BRA director Stephen Coyle, now with the AFL-CIO in Washington D.C., was instrumental in helping Genzyme choose its Allston site says McLachlan. One of the selling points of the site, says McLachlan, was Coyle's skill in expediting the administrative process.

While no major out-of-state company has yet been lured to Massachusetts, the state hasn't lost any large companies to other states either. Goldberg adds that there are more and more startups coming in every day. And industry executives agree that the Genzyme decision sends out a positive message to other Massachusetts-based biotech firms. Says James Vincent, president of Biogen, which will probably be going through a similar siting decision in a year or so, "In a broader sense, more important than the hard financial issues, I think most of us had to see the state become business friendly. Weld was aggressive in meeting or attempting to meet [Genzyme's] conditions."

Tocco talks a pretty aggressive and optimistic line, too. "Once we get to economic parity [with other states], no one can touch us. Massachusetts has turned the corner, we're on the way back."

–Michelle Hoffman



Beantown biotech boom? Boston's greater metropolitan area ranks behind only the two California behemoths, the Bay Area and greater Los Angeles, in biotech revenues.