grants, the "forward funding or multiyear funding" scheme, which would have forced NIH to hold on to a certain portion of 1987 money for spending in 1988.

OMB officials insist that they do not get involved in making decisions on scientific emphasis or merit, but stick strictly to numbers. The nation simply cannot afford to spend as much as Congress would like, OMB argues. Although OMB has failed over and over in the past 5 years to turn this message into fiscal fact, it claims to have shaped the debate and put the spotlight on issues that need attention, such as the rate of inflation in grant costs, the correct way to count NIH's grant liabilities (by the total number of grantees), and the drain on research imposed by institutional "indirect cost" fees.

Representative Natcher, who plays a low-key but powerful role in appropriations, blames OMB for the Administration's failure to support biomedical research more generously. In a congressional debate on 5 August he said: "I do not believe that President Reagan knows that some of these reductions are in [his own budget]. . . . No President I have served with, and I have served with seven of them, none of them knows all of these items and agencies."

In fact, NIH, more than other science agencies, is somewhat cut off from the executive decision process. NIH is not asked to make a direct presentation to OMB. The director of NIH presents a budget to the assistant secretary for health, who usually cuts it and sends it along to the secretary of health and human services, who cuts it and presents it to OMB. It can be difficult to communicate across this great bureaucratic divide. However, OMB staffers do make selected visits to the NIH campus to get information firsthand.

An author of OMB's recent grant-limiting proposals, NIH budget examiner John Glaudemans, is regarded as both brilliant and arrogant. Representative Natcher's staff viewed him as an able adversary, "razor sharp," one staffer said. "As much as people in the scientific community love to attack the guy, I've got to say one thing: he knew how to do his job, and his job was to cut the heck out of the NIH budget," says Bradie Metheny of Delegation for Basic Biomedical Research, who adds that he maintains "real respect" for Glaudemans. "He's as clever as they come." He is said to have claimed special insight into NIH because his father works there. Glaudemans recently was promoted to another post within OMB and no longer handles the NIH account directly.

This fall when the Secretary of Health and Human Services makes his budget pitch—including a recommendation for NIH—the numbers will go first to Richard Jacob, a new man on the job. From him, the budget passes to Barry Clendenin, director of OMB's Health and Social Services division, then on to David Kleinberg, a deputy associate director, thence to the deputy director, and finally to the director, James C. Miller III.

The OMB presents the whole budget, with options laid out, to the President in November. Decisions are made and agencies are given 3 days to appeal. Final changes are limited by the printing schedule, which calls for publication in the first week of January.

It is a complex and multilayered process in which at least three budget years are being actively reviewed at any given moment. In recent times, the process has been confounded by the wide gaps between the President's low budget assumptions for NIH and the high, actual levels of funding provided by Congress. Because new budget levels are tied to the previous year's appropriation, and because appropriations now come very late in the year (sometimes November), the budget-writing business has become increasingly difficult and, at the same time, unrealistic.

But no matter how complex and thorny the barriers may have become, NIH thus far has been able to find its way to the Treasury. ■ ELIOT MARSHALL

# Biologics Gain Influence in Expanding NCI Program

*Forged in the political climate that surrounded early enthusiasm for interferon as a general cancer treatment, the NCI's biological response modifier program continues to evolve*

INTERLEUKIN-2, a potent biologic agent that stimulates a spectrum of immune responses, today generates a mixture of optimism and controversy as a cancer therapy. Some patients with advanced or drug-resistant tumors respond to interleukin-2 (IL-2). But it can be highly toxic, and critics believe that its promise has been overstated.

Interferon alpha is not the universal magic bullet against cancer that it seemed to be 10 years ago. But interferon is particularly effective against hairy cell leukemia and also seems to be useful against low-grade lymphoma, chronic myelogenous leukemia, and Kaposi's sarcoma, a form of cancer common in patients with AIDS.

Tumor necrosis factor, a protein-like compound, also stimulates a variety of immune responses. About 15 years ago, researchers demonstrated its ability to kill tumor cells in animals. Now they find that, in the presence of interferon gamma, the antitumor effects of both biological compounds increase.

These are among about a dozen biological agents that have become the focus of the National Cancer Institute's (NCI) newest research effort in cancer treatment, the Biological Response Modifier Program. The mandate of this $40.4-million endeavor is to identify natural compounds that can be used to increase the body's response to cancer. The program came into being as an administrative entity in 1981 through a combination of intense political pressure and scientific readiness. Today, NCI researchers outside the program also study the active biological compounds, bringing the estimated total funding in this area to the $168.6-million mark for 1987. In addition, researchers at the National Institute for Allergy and Infectious Diseases are seeking therapeutic roles for some of the compounds in treating patients with AIDS.

"After many years of fitful research in the area of biological therapy dating back to the last century, it finally appears as though biological therapy is joining surgery, radiation therapy, and chemotherapy as a legitimate tool in the cancer specialist's armamentarium," said program director Daniel Longo at a 1985 meeting of the National Cancer Advisory Board. He refused to be

interviewed for this article.

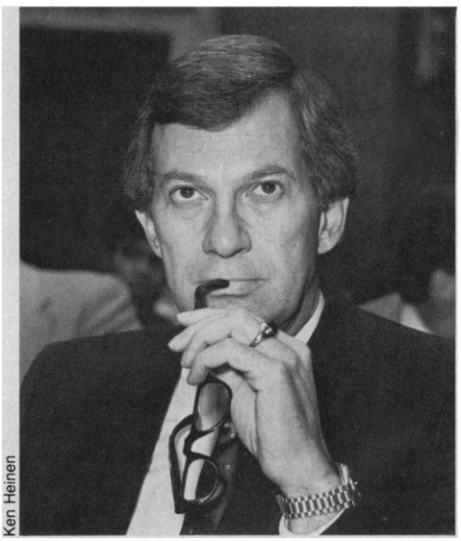
It is difficult to trace precisely the chronology of events that led to the formation of the biological response modifier program, because each person recounts what happened with a different emphasis. But it is clear that in the late 1970s, when hopes were high that interferon would cure many, if not all, types of cancer, Mary Lasker of the Albert and Mary Lasker Foundation in New York City and Mathilde Krim, now of the American Association for AIDS Research in New York, lobbied hard for a special interferon program. They pressured members of Congress and scientists on the National Cancer Advisory Board to urge NCI to purchase as much interferon as possible and study its effectiveness as a cancer therapy.

Congress responded by giving the institute $13.5 million in 1979, an award that became the major financial impetus for initiating the biologics program. According to Robert Oldham, program director from 1981 to 1984 and now chairman of Biotherapeutics, Inc., and director of the Biological Therapy Institute in Franklin, Tennessee, NCI's initiation of the biologics program "was a somewhat tardy response." The institute probably should have been testing and developing biological compounds as much as 5 years earlier, he says. Some of them—interleukin-2, interferon, and tumor necrosis factor, for instance—had been identified well before the start of the program.

Current NCI officials acknowledge the congressional boost but stress that the institute itself had an early and strong interest in building the biological response modifier program. "In 1977, following a seminar on interleukin-2, Bob Gallo [of NCI who discovered interleukin-2] came to me and said that one day interleukin-2 and other lymphokines would have to be brought to clinical trials," says Vincent DeVita, Jr., current director of NCI, who was director of the Division of Cancer Treatment in 1977. DeVita asked Enrico Mihich of Roswell Park Memorial Institute in Buffalo to lead an advisory subcommittee to look into the idea.

"Then, in 1979, interferon landed on us," says DeVita. "What ensued was a debate involving Congress and the National Cancer Advisory Board." The argument centered around whether NCI should buy large amounts of interferon, which at the time could not be manufactured in quantity. The 13-member group headed by Mihich recommended that NCI invest much of the congressional $13.5 million as well as institute funds in basic and clinical research on biological response modifiers rather than in the purchase of vast quantities of interferon.

Meanwhile, the concept of the biologics program was being resisted by some cancer



Ken Heinen

**Vincent DeVita, Jr.** *"I see biological response modifiers as another manifestation of the advances in molecular medicine."*

specialists who favored more traditional cancer therapy, says Oldham. The new program also represented a shift away from the NCI treatment mainstay of the 1960s and 1970s. "The primary gestalt of the NCI's treatment program for 20 years was chemotherapy," says Oldham. "There was a tremendous affection, a major prejudice really, among people who make decisions that they would ultimately find a drug that would be generally useful in treating many kinds of cancer."

But DeVita notes that, even before the biologics program officially began, NCI had scaled down its funding for the development of chemotherapeutic agents. "By the time the biologics program started, the chemotherapy program had been reduced from about $68 million a year to about $42 million," he says. "So it was already declining. The emphasis in chemotherapy was initially to address the treatment of metastatic disease, to get rid of circulating cancer cells. But biologics awaited scientific events that took place in the mid- and late 1970s."

Like Oldham, Ronald Herberman, director of the biologics program in 1984 and 1985 and currently director of the Pittsburgh Cancer Institute and professor at the University of Pittsburgh School of Medicine, remembers difficult early times. "I think that a lot of money was put into the program initially and then there was very slow or almost no growth for a period of years," he says.

Despite initial stagnation, the recent budget for the biologics program has ballooned from about $26.5 million in 1985 when Herberman left to about $40.4 million for 1987—an increase of more than 50%. During the same period, the total NCI budget also grew, making it easier to expand the new program. "The budget increases in the biological response modifier program have pretty much followed and, in some cases, exceeded the increases in the overall NCI budget," says Bruce Chabner, director of the Division of Cancer Treatment, which includes the biologics program.

Carl Pinsky, chief medical officer for extramural research in the biologics program at NCI in Frederick, Maryland, notes that when the $40-million budget for developing many different biological compounds is compared to the $100 million or so that a private company spends to develop a single drug, the NCI investment is not all that large. The estimated increase for the program in 1988 is only $2.2 million. However, this figure may change after the real budget for the institute is known, says Chabner. It will also increase if NCI receives additional funds to test biologics in AIDS.

Organizational changes are another indication that the biological response modifier program is evolving. "We created an entire molecular biology branch and separated the clinical branch from the cellular immunology branch," says Chabner. These changes in intramural laboratories should give the program added scientific expertise and allow it to expand into new areas, he says.

Chabner engineered a different kind of reorganization this spring when he recommended that the so-called decision network committee should be dissolved and replaced. This internal body decided which biological compounds should have priority for toxicology testing and clinical trials. Now the responsibility is to be shared with a parallel committee in the Developmental Therapeutics Program that made previously similar decisions about chemotherapeutic agents.

"The concern that I have is that the shift in this decision-making process is to a group in which expertise in biological response modifiers is not well represented," says Herberman. DeVita himself questioned the change at first but is now convinced that the smaller restructured committee does have the necessary expertise and that it will streamline the process of getting all types of cancer therapy into clinical trials.

The clinical capabilities of the biologics program have also evolved. Since 1985, the number of patients at the NIH Clinical Center has expanded as has the number of clinical trials nationwide, although DeVita wants to include even more patients, especially in the later phases of clinical testing. And in 1984 Herberman introduced a novel system for determining the appropriate therapeutic dose of a biological compound.

"In contrast to a chemotherapeutic drug, the highest dose tolerated with a biological compound is not necessarily the most effec-

tive dose," says Herberman. In order to find the most effective dose of a biological agent, which is often lower than the maximum dose that a person can tolerate, Herberman instituted a two-stage testing process. Phase Ia trials are designed to determine the maximum *tolerated* dose, which corresponds to phase I trials for chemotherapeutic agents. The unique aspect of the process is the phase Ib trial, which is designed to identify the maximum *effective* dose of a biological compound.

Another unusual feature of the biologics program is a method for prescreening biologics, a stage of testing that precedes testing the compound in patients. The procedure includes a series of biological assays—performed in vivo in animals or in vitro on B or T lymphocytes, natural killer cells, or monocytes—to see if a compound has biological activity, says Gregory Curt, deputy director of the Division of Cancer Treatment. If it does, then the decision network committee decides whether to invest the necessarily large amounts of money in toxicology testing and further analysis of the compound.

Aside from the variety of changes within the biologics program, new findings in scientific research are its driving force. The use of genetically engineered forms of biological compounds, for example, is a new technology that has in some ways helped to shape the research focus of the program, says Pinsky. Recombinant products reduce problems of lot-to-lot variation and questions of purity that had often complicated early trials with materials extracted from living tissues, he says.

A prime example is interferon alpha, which so far is the only biological compound the Food and Drug Administration has licensed for treating cancer. Ten years ago, supplies of interferon were very expensive because it had to be extracted from biological material. Now private companies make large quantities of the compound. It is used to treat patients with hairy cell leukemia, 500 to 1000 of whom are diagnosed each year as having the once-fatal illness.

Steven Creekmore, the extramural program director, predicts that future therapies will include combinations of biologics. "Biological compounds all interact with one another in the body," he says "so it would be bizarre for us to focus on a single factor as the key." For instance, the future of interleukin-2 may lie with a modified treatment protocol. "I expect that IL-2 will ultimately be used as one component in a cocktail of biological compounds, possibly with interferon or monoclonal antibodies," he says.

Interleukin-2 has simultaneously been hailed as the beginning of a new era and criticized for its toxicity (*Science*, 9 January, p. 154). Steven Rosenberg in the Clinical Oncology Program at NCI, reported that IL-2 produces at least a 50% reduction in tumor size in about 35% of patients with advanced or drug-resistant metastatic melanoma or kidney cancer.

In fact, adverse side effects seem to be greatest with Rosenberg's published treatment regimen. His patients have received large doses of either IL-2 alone or IL-2 in combination with their own LAK cells, cells previously removed in a blood sample and converted to *l*ymphokine-*a*ctivated *k*iller cells by treatment with IL-2. Severe side effects including low blood pressure, fluid in the lungs, fever, anemia, and even confusion may result. Coping with such toxic reactions requires costly intensive care treatment, making IL-2/LAK therapy a target for criticism. Toxicity seems to be related to the dose and the timing of treatments, and researchers at NCI and elsewhere, including Oldham, are testing other regimens.

Treatment with biological compounds may soon be combined with other, more standard forms of therapy. For example, many patients with breast cancer or adenocarcinoma initially respond well to drug therapy but then relapse because not enough of the drug can be given safely to completely destroy the tumor cells. "It may be possible with these patients to use factors that enhance bone marrow growth in combination with chemotherapy," Curt says.

The major toxic effect of chemotherapy is bone marrow suppression, so by enhancing the growth of bone marrow cells it might be possible to give more drug and increase the chances that tumor cells are completely destroyed. Particularly useful in this context, according to Curt and Creekmore, could be GM-CSF and G-CSF, the colony-stimulating factors that enhance granulocyte and macrophage division or granulocyte division. (The same rationale is being planned in AIDS patients who receive AZT, an antiviral drug that causes bone marrow suppression; see *Science*, 1 May, p. 517.)

Although many of the biological compounds now being evaluated in the program act in some way to modify the responses of the immune system, others function differently. For instance, molecular fragments of laminin, a complex protein that normally exists in the space surrounding a cell, may be useful for inhibiting tumor cell attachment and metastasis. In addition, compounds important during normal human development might also have therapeutic effects. Mullerian inhibitory substance, for example, which in males prevents the upward migration of embryonic tissue that otherwise forms a uterus and ovaries, is very potent in its ability to kill ovarian cancer cells in vitro.

Future research directions for the biologics program will include specifically targeted areas, says Pinsky. Program announcements for extramural research last year called for proposals on a range of topics: the mechanism of action of LAK cells; factors that regulate cell development animal models for testing biological compounds; oncogene products in cancer therapy; interactions between the nervous and immune systems in cancer; and ways of conjugating tumor-specific monoclonal antibodies with agents that may destroy tumor cells.

Within the past few months, program officials requested applications for immunological studies on p-170, a multidrug resistance protein that occurs on the surface of certain tumor cells that are resistant to chemotherapy. In response, researchers will devise ways of using immunological techniques to interfere with the action of p-170, which apparently ferries certain antitumor drugs out of tumor cells, thereby diminishing their capacity to get rid of the tumor.

Program planners also targeted the development of a group of biological substances—colony-stimulating factors and interleukins, in particular—that would increase bone marrow production. And they called for studies on how to "manipulate the suppressor arm of the immune system to get antitumor effects," says Pinsky. "This has not necessarily been a successful area in cancer therapy and we want to stimulate some research on it."

Herberman notes that things have changed. "There certainly has been an evolution—within the NCI and outside the institute—to accept biological response modifiers as an additional modality for cancer therapy," he says. Chabner assesses the present. "The impact of biologics in patients with cancer is limited so far." Curt looks to a bright future. "The use of growth factors is going to revolutionize medicine as we know it—and not just in cancer," he says. "There is no question about it." DeVita plans for transition. "I see biological response modifiers as another manifestation of the advances in molecular medicine," he says. "I think it is a program that will become very different in time, and that's good. I think there is a danger in settling down." ■

**DEBORAH M. BARNES**

ADDITIONAL READING

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