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# MEDICAL ONCOLOGY IN THE 1990s

Robert J. Spiegel, M.D.

*The pharmaceutical industry has identified oncology as a major therapeutic area for development, and is building its research and development base accordingly.*

**R**ecent developments in molecular biology, as well as advances in our understanding of tumor biology and the immune system, promise to make the 1990s an extremely exciting decade in medical approaches to cancer. Historically, medical oncology has relied on the empiric use of potent cytotoxic agents to kill cancer cells and, occasionally, on hormonal manipulation of tumors that were known to be hormone sensitive.

## Where We Were

Traditional chemotherapeutic approaches were highly successful in a few select cancers, but have not produced long-lasting remission in large percentages of patients with most tumor types. In many cases, chemotherapy pushed the therapeutic index of pharmacologic treatment to extremes not tolerated in any other therapeutic area.

Although there is still enthusiasm for the pursuit of enhanced biochemical modulation, the approach of simply increasing doses to maximum toleration or trying new combinations of known drugs, began to lose its allure in the 1970s and the 1980s. There was an increased recognition that just trying new combinations of available agents was unlikely to yield significant improvements in therapeutic outcome.

## Where We're Going

We enter the 1990s with a newly enhanced armamentarium in hand, and new targets for drug development in the wings. The major areas of interest that are spurring a new level of enthusiasm include: increased understanding and identification of oncogenes as potential targets for new drug development; a new understanding of drug resistance and targeted programs designed to overcome drug resistance; and the coming of age of immunotherapy with alpha interferon as

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the first approved biological for oncology.

Novel approaches for recruiting the body's immune system to eradicate cancer cells, including interleukin-2 and monoclonal antibodies, are in the wings. Added to this is the explosive growth in our understanding of the immune system's regulatory effector cells and their controlling factors, and the availability of agents that can literally titrate patients' hemoglobin, granulocytes, and macrophages at the physician's discretion. Finally, hormonal therapy of cancer has advanced with the introduction of designer drugs that can provide, for example, non-steroidal anti-androgens (e.g., Eulexin) or other specific endocrine blockers.

## Partners in Research

It should not be surprising that this new scientific springboard has forged a new relationship between the government/academia/industry partnership that has always existed in oncology. The National Cancer Institute (NCI), leading cancer centers, and industry have now emerged

as intertwined partners in the development of these technologies. Even the Food and Drug Administration (FDA) has become a more active participant in early drug development; it has restated its desire to work in concert with new drug sponsors to ensure that new entities can be brought from the test tube to the clinic as rapidly as possible.

## Industry's Growing Interest

The pharmaceutical industry has identified oncology as a major therapeutic area for development, and it is entering the 1990s in a very different posture than a decade ago. The most visible and publicized aspect of this change is the emergence of dozens of start-up biotechnology companies whose research bases are built upon monoclonal antibodies or recombinant DNA technology, with diagnostic or therapeutic targets in oncology. However, many of the established pharmaceutical companies have also made oncology a major research and development program in the last decade.

Schering-Plough's participation in oncology research may serve as an example of the new environment and the new opportunities being seized upon by corporate research groups, in participation with the NCI and the academic community. The company entered the 1980s as a well-established pharmaceutical concern with a strong franchise in anti-infectives, allergy, and dermatologics, but no particular basic or clinical research group was dedicated to oncology.

The company is now entering the 1990s with four oncology products in the clinic, as well as a fifth antifungal compound that has exciting potential applications in cancer. Two of the oncology products have already been successfully marketed—Intron A (alpha interferon) and Eulexin (flutamide).

The company's commitment to



oncology is evident in its growing support of the DNAX Research Institute in Palo Alto, CA. Through this institute, the company is identifying new lymphokines through molecular biology research, and it is operating an in-house tumor biology program that is targeting oncogenes, multi-drug resistance, and mechanisms of metastasis. More than 20 percent of Schering-Plough's R&D budget is now committed to biotechnology.

## The Alpha Interferon Parable

Alpha interferon has previously been identified as a pioneer product for biotechnology, and indeed, the history of the development of Intron A may well serve as a parable.

Alpha interferon began the 1980s on the cover of *Time* magazine, where it was touted as a potential cancer cure. Notably, this media hype preceded any industrial involvement in the development of alpha interferon. Nonetheless, this unsolicited publicity set expectations that no drug could realistically fulfill.

However, after a period of skepticism, alpha interferon has emerged as one of the most successful oncologic agents now available. It is currently marketed in 42 countries for 15 anticancer and viral indications, and its full potential is still being explored in multiple, ongoing studies.

Alpha interferon's potential as a potent growth suppressant and possible differentiation agent is just beginning to be realized in such hematologic conditions as multiple myeloma, chronic myelogenous leukemia, and non-Hodgkin's lymphoma. Moreover, it continues to be

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extensively studied as monotherapy and in combination with other agents in a variety of solid tumors, both as primary treatment and as potential adjuvant therapy.

In addition, very exciting results describing the remarkable activity of alpha interferon in chronic viral hepatitis were recently published in the *New England Journal of Medicine* (22:1506,1989). It can result in significant reductions in liver enzymes, as well as improvement in liver histology. These results ensure that alpha interferon is likely to be a major product for many years.

## Other Therapies

For those companies who began developing recombinant proteins in the 1980s, each new therapeutic candidate helps make the foray into the biotechnology arena that much easier. With this in mind, Schering-Plough is now actively pursuing the development of recombinant granulocyte macrophage stimulating factor (GM-CSF). This product, which is being developed in cooperation with Sandoz Pharmaceuticals, has the potential to rapidly restore the body's immune system following chemotherapy or bone marrow transplantation. In addition, it might have direct anti-tumor activity, based on its ability to stimulate and activate macrophages. This product is now undergoing extensive clinical trials to determine its full role, and a

Product License Application was filed with FDA in January 1990 for its use in the treatment of patients with low white blood cell counts.

Schering-Plough is also developing interleukin-4, which has a variety of immunologic effects with significant promise in many oncologic settings.

Finally, the company's prostate drug, Eulexin, approved in the United States in 1989, has been demonstrated to extend survival when used in combination with the LHRH agonist leuprolide. New studies are now examining the potential role of Eulexin in early stage prostate cancer and in benign prostatic hypertrophy (BPH).

## Summary

These examples demonstrate how one major pharmaceutical company has rapidly become involved in and committed to oncology as a major area of development. Many other pharmaceutical companies are also increasing their commitment to this field. These efforts, together with those of the many focused biotechnology companies, and the advances being made in academia and through the NCI, promise to make the 1990s the most exciting decade yet for the development of novel therapies of cancer.

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