Journal of Cellular Biochemistry, Supplement 22:254–259 (1995)

Fostering Chemopreventive Agent Development: How to Proceed?

James L. Mulshine, MD

Biomarkers and Prevention Research Branch, Early Detection and Community Oncology Program, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Rockville, MD 20850-3300

Abstract Improved molecular-based detection of early epithelial cancer creates an opportunity for selective pharmacologic agents to arrest the development of emerging cancers. Developing a successful prevention approach to cancer control could eventually lead to a significant decline in cancer mortality rates; progress depends on the amount of resources committed to this area. Most major prevention trials are federally supported due to their size, duration, and cost. Much of the initial developmental cost for advanced cancer treatment agents was supported by the pharmaceutical industry. Developing a cancer treatment agent is perceived as more clearly defined and achievable than for prevention agents. Preliminary discussions with representatives of the pharmaceutical and biotech industry have identified a number of barriers to chemoprevention product development. Researchers agree that a number of promising agents are being passed over for expeditious development due to the uncertainty associated with chemoprevention drug development. The major factors affecting this circumstance are considered, including cost of clinical trials, absence of a positive model, and inability to project liability exposure.

Similar problems were encountered in the area of childhood vaccine development. Insights from that process may have applicability to prevention drug development. Resolving these problems now can have a significant effect on the rate of progress in this promising new approach to cancer control.

Key words: Breast cancer, chemoprevention, intervention, lung cancer, promotion

DEFINING THE PROBLEM

Since the seventies, the lack of success in treating advanced cancer has lead to a systematic trend to treat earlier stages of the disease [1,2]. With the limited success of even adjuvant and neo-adjuvant approaches [3], the need to intervene even earlier is evident. Recent efforts with tamoxifen and retinoids have highlighted the possibilities in this regard. Individuals who develop a first epithelial cancer are at increased risk of developing additional cancers in the remaining parts of the afflicted organ. Trials in which women receive tamoxifen as adjuvant therapy for locally advanced breast cancer show a significant reduction in the rate of new contralateral primary breast cancers [4]. The success of tamoxifen in suppressing additional breast cancers is thought to be due to its neutralizing effects on the breast cancer-promoting properties of estrogen. The ongoing Breast Cancer Prevention Trial which randomizes 16,000 women to receive tamoxifen or placebo is designed to evaluate the exact benefit [5]. Due to the magnitude of the chemopreventive benefit seen in the tamoxifen adjuvant trials, many investigators expect major benefits will be seen in the ongoing tamoxifen prevention trial. Similar reports from the

Address correspondence to James L. Mulshine, MD, Biomarkers and Prevention Research Branch, Early Detection and Community Oncology Program, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, 9610 Medical Center Drive, Room 300, Rockville, MD 20850.

groups at M.D. Anderson Cancer Center (Houston, TX) and Milan have suggested that retinoids may suppress new aerodigestive cancers in patients already successfully treated for a first aerodigestive cancer [6–9]. If ongoing trials confirm that intervention helps to control early cancer, there may be significant promise for reducing cancer mortality. The ability to detect the early phase of epithelial cancer is improving as a by-product of the molecular diagnostic progress [10–12].

The gap between scientific/medical possibilities and research investment in prevention constitutes a critical impediment to the development of more effective cancer management measures leading to improved cancer outcomes. This manuscript attempts to summarize the basis for this situation.

Despite a maturing knowledge of molecular carcinogenesis, the pharmaceutical companies have limited interests in developing prevention agents. A number of problems have been cited as contributing to this situation. The actual development of a new cancer even in a "high risk" population is uncommon. This means definitive trial designs require large populations with long study durations. A manufacturer may invest as much a $150,000,000 in the process of sponsoring a new drug through the approval process [13]. As summarized in Table I, clinical trials to evaluate intervention drugs take longer to complete than conventional chemotherapy trials and may routinely involve more biological monitoring [6], increasing the interval from development of a new drug to final Food and Drug Administration approval. Consequently, direct costs are high; the cost of the "clinicals" and the capital invested in the effort will be greater. Since the approval process takes longer, the current length (17 years) of patent protection would be functionally shorter for an intervention drug. Current patent protection may not be adequate for drugs that are already available or for new drugs that take a long time to show clinical benefit. This would again compromise a sponsor's ability to recover an initial financial investment. A pharmaceutical company can only undertake the massive cost of new product approval if it appears likely that the investment will be rewarded. For these reasons, the need to invest large dollar amounts in prevention trials has discouraged significant pharmaceutical industry support.

Currently there are no approved prevention drugs so the precise path to a successful product is unclear. The requirements for regulatory review are not established. The cost of performing toxicology testing on a prevention compound is likely to be much more expensive since chronic use of a chemoprevention agent by high-risk subjects would be the rule. Industry experience with breast implants points out the volatility of new product development. Before a company can responsibly invest a large amount of capital, it also has to develop a cost plan that anticipates all significant expenses related to the product development effort. Product liability awards for other preventive products such as vaccines have traditionally been large [14]. Both the large number of participants required for prevention drug validation and the typical good health of individuals receiving an intervention compound indicate that intervention agent manufacturers would have vast downstream exposure for product liability suits. This risk is particularly difficult in a business environment since no reasonable boundaries on the risk-exposure can be developed, and the liability exposure of a manufacturer to adverse outcomes is likely to be much more problematic than is currently experienced with cancer treatments.

These problems are exacerbated by the current state of biotech industry funding. From a high of over $3.6 billion invested in this industry in 1991, only $0.7 billion have been invested through the

TABLE I. Distinctive Features of Intervention Trials

Large trial size
Long study duration
Potential for significant product liability exposure
Volatility with reimbursement issues
Lack of successful development model

TABLE II. Cancer at a Crossroads
A Report to Congress for the Nation: Executive Summary

1. Current health care reform proposals are devastating to the War on Cancer by denying resources for research and quality cancer care.

2. The National Cancer Program suffers from an absence of national coordination of cancer-fighting efforts in the public, private, and voluntary sectors.

3. Many people in this country, especially the poor, elderly, and uninsured, receive inadequate cancer care.

4. Current laws, public policy, and government regulation undermine cancer prevention, treatment, and control efforts.

5. Failure to support translational research hinders rapid development of cancer-fighting advances.

6. Current investment is insufficient to capitalize on unprecedented opportunities in basic science research.

first eight months of 1994 [13]. This decrease in funding reflects both underlying economic conditions and a maturation of realistic expectations by the investment community. Intervention research is only a small percent of the total portfolio of the biotech industry. In light of the previously discussed issues, companies developing intervention agents do not have sufficient momentum to overcome the current downward trend in global biotech funding.

A further complication is that not all of attractive intervention compounds are new drugs. For example, aspirin enjoys functional orphan status relative to its use as an intervention compound for colon cancer because it is an old drug readily available over the counter [15]. No industry sponsor will assume the substantial cost of a validating clinical trial with no possibility of market protection. This may leave the federal government as the sole institution able to conduct a definitive aspirin intervention trial. The cost of the tamoxifen intervention trial is on the order of $60,000,000. Since industry now invests more in pharmaceutical research and development than the government, it would be unfortunate if those resources could not be recruited to accelerate the development of these new and potentially more effective agents.

These challenges were noted in the recent evaluation of the National Cancer Program by a subcommittee of the National Cancer Advisory Board (NCAB) [16]. The report, entitled "Cancer at a Crossroads," is summarized in Table II; its conclusions reinforce the issues already discussed. If support for clinical investigation is not provided as part of the health reform process, the feasibility of conducting prevention trials is further eroded. The major cost of developing a new drug is incurred during Phase III clinical trials. If health care reform eliminates cost sharing of this process, significant new funds will have to be identified or these agents will not be developed. The subcommittee concluded that current laws, public policy, and government regulation undermine cancer prevention and control efforts. Combined with the previously mentioned patent issues, this highlights the lack of coordination for these complex issues. Clearly, we need to work on better characterizing these problems so that measures to improve this situation can be initiated.

The NCAB report communicates grave concern about adequate support for translational research, which encompasses a range of efforts applying basic science information to new approaches in clinical care. Most ongoing prevention research falls into this general category. Again because many current prevention research opportunities are the by-product of new concepts and employ new research tools, funding mechanisms to support these efforts are not well established. The report notes that many of the new prevention efforts require multiple professional disciplines including clinical, basic science and epidemiology. Translational scientists who appreciate a range of these disciplines are rare. Establishing training paths to increase this talent pool is fundamental to success. Many more trained prevention researchers are clearly needed in industry as well as in academe.

WORKING TOWARDS A SOLUTION

A formidable range of issues must be coordinated to permit integrating intervention agents into clinical practice, but precedence is provided by the experience of developing childhood vaccines. Responding to concerns that production, distribution, and administration of childhood vaccines was suboptimal, the Institute of Medicine conducted a comprehensive analysis; the results, briefly summarized for this discussion, have been recently published [14].

The utility of vaccines is beyond dispute. Nevertheless, each year over two million deaths and five million cases of disability occur worldwide from diseases that are preventable by vaccination. This is a major problem in the United States—our rate of vaccination is lower than many developing nations. The logistics of vaccination could be greatly simplified if they were formulated to reduced the number of requisite administrations and did not require refrigeration. Despite major scientific breakthroughs in relevant areas, the public health community felt that refinement of vaccine technology was not occurring. Large numbers of fatalities occur from other infectious diseases for which no effective vaccine yet exists. A group of concerned professionals developed a focus group called the Children's Vaccine Initiative (CVI) to address shortcomings in this area. The CVI established as their primary goal the development of an affordable, heat-stable, multiple-antigen, single-dose

vaccine. CVI organizers were aware that no single entity had the resources to achieve this goal; so they organized a forum to examine the strategic, logistic, and policy issues relevant to the industrial development and introduction of the proposed CVI vaccination product. Areas of analysis included quality control, global vaccine supplies, and epidemiologic studies to monitor the need for the new product. The Institute of Medicine (IOM) was asked for advice on domestic participation in this process. The IOM mandate included characterization of economic, legal, regulatory, policy, and other factors which, in any way, influenced the development, production, and distribution of vaccine. The IOM was also supposed to recommend ways to enhance cooperation and participation among relevant domestic sectors to help realize the goals of the CVI.

Finding no direct connection between research and development on one hand, and the use of vaccines on the other, was most disturbing to the IOM committee. The various decision makers do not work together; in fact, they respond to different pressures. Lack of a domestic strategy has impeded full childhood vaccine development in the United States. In the US, only very large agencies buy vaccines, leading to an austere commodities price structure. Little new research is being done; new product development has been stifled. The cost of producing a vaccine is extraordinarily expensive in terms of physical plant and regulatory review. Due to these conditions, the IOM study concluded that it is unreasonable to expect a commercial manufacturer to pursue vaccine development. The anticipated costs associated with research and development may be too high, patent issues may be too complex, the licensing process may present unacceptable obstacles and the risk of liability may appear too great.

The IOM committee noted that "when stable, predictable and long term returns can be expected, commercial vaccine manufacturers have demonstrated their ability to manage and oversee the entire spectrum of activities required to take a vaccine from the point of proof of principle to the point of production and distribution". The committee concluded that successful US participation in the effort will depend on effective cooperation and collaboration among government, universities, and the private sector (the IOM committee specified the private sector, both biotechnology firms and established vaccine manufacturers, as the most important participants). The committee recommended establishing an entity to advance production and procurement of new and improved vaccines with high public health benefit. To be successful, the entity would have to balance its public health mission and its entrepreneurial activities. This would require broad representation on its planning board. The IOM committee specifically stated that no federal agency has the multidisciplinary capability required to manage the integrated development, production, and procurement of needed vaccines. The entity envisioned by the IOM committee would be responsible for cultivating a more fertile environment for targeted technology development in this critical public health area.

Parallels between vaccine development needs and development of intervention agents are direct and indisputable. The process of ameliorating the current situation with intervention drug development could be structured in precisely the same fashion as was proposed for vaccines. Most crucial is to initiate dialogue to define the problems of prevention drug development so that all relevant sectors understand its dimensions. A strategic effort in the development of new cancer chemopreventive agents similar to that used by the IOM to resolve vaccine development problems should be pursued. Societal frustration with the slow pace of progress in cancer research is approaching historic proportions. Creating an environment in which these new drugs can be expeditiously developed and tested is one of the most important challenges facing the cancer research community today.

ACKNOWLEDGEMENT

The ideas and issues summarized in this manuscript evolved during a series of conversations and small meetings with a number of concerned professionals including: Thomas May, Gary Kelloff, Gail Shaw, NCI; Gregory Burke, FDA; Charles Van Horn, Office of Patent and Trademarks; Brian Markison, Bristol-Myers Squibb Pharmaceutical Research Institute; Thomas Griffin, Hoffman LaRoche Pharmaceuticals; Michael Sherman, PharmaGenics, Inc; Allen Fox and Daniel Kiser, Fox, Bennett and Turner; Peter

Hutt, Covington and Burling; Mary Wilson, Nixon, Vanderbye; Edward Yates, Johns Hopkins University; John Magnani, GlycoTech; and Waun Ki Hong, University of Texas M.D. Anderson Cancer Center.

The opinions and the assertions contained herein are the private views of the author and are not to be construed as the official statement or as reflecting the views of the Department of Health and Human Services.

REFERENCES

1. Schabel FM Jr: Rationale for adjuvant chemotherapy. Cancer 39:2875–2882, 1977.
2. Griswold DP: Body burden of cancer in relationship to therapeutic outcome: Consideration of preclinical evidence. Cancer Treat Rep 70:81–86, 1986.
3. Beardsley T: A war not won. Sci Am 130–138, 1994.
4. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 339:1–15, 1992.
5. Nayfield S: Tamoxifen's role in chemoprevention of breast cancer: An update. J Cell Biochem 20 (Suppl), this issue, 1995.
6. Lippman SM, Benner SE, Hong WK: Cancer chemoprevention. J Clin Oncol 12:851–873, 1994.
7. Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Beyer RM, Schantz SP, Kramer AM, Lotan R, Peters J, Dimery IW, Brown BW, Goepfert H: Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 323:795–801, 1990.
8. Benner SE, Pajak TF, Lippman SM, Earley C, Hong WK: Prevention of second primary tumors with isotretinoin in squamous cell carcinoma of the head and neck: Long term follow-up. J Natl Cancer Inst 86: 140–141, 1994.
9. Pastorino U, Infante M, Maioli M, Chiesa G, Buyse M, Firket P, Rosmentz N, Clerici M, Soresi E, Valente M, Belloni P-A, Ravasi G: Adjuvant treatment of stage I lung cancer with high-dose vitamin A. J Clin Oncol 11:1216–1222, 1993.
10. Mulshine JL, Shaw GL, Cuttitta F, Scott F, Avis I, Treston AM, Linnoila RI, Birrer M, Brown P, Gupta K, Tockman MS: Applications of biomarkers for lung cancer early detection. In Fortner JG, Rhoads JE (eds): "Accomplishments in Cancer Research." Philadelphia: J.B. Lippincott Co., 1992, pp 204–216.
11. Mulshine JL, Linnoila RI, Magnani JL: Applications of monoclonal antibodies in the management of lung cancer patients. Chest Surg Clin N Am 1:153–189, 1991.
12. Mulshine JL, Tockman MS, Scott, F, Gupta PK, Shaw GL: Global strategies for the early detection of epithelial cancers. In Srivastava S, Lippman SM, Hong WK, Mulshine JL (eds): "Early Detection of Cancer Molecular Markers." New York: Futura Publishing Co., 1994, pp 13–19.
13. Carey J: Biotech. Business Week. 3391:84–88, 1994.
14. Mitchell VS, Philipose NM, Sanford JP (eds): "The Children's Vaccine Initiative. Achieving the Vision." Washington DC: Natl Acad Press, 1993, pp 1–145.
15. Earnest DL, Hixson LJ, Finley PR, Blackwell GG, Einspahr J, Emerson SS, Alberts DS: Arachidonic acid cascade inhibitors in chemoprevention of human colon cancer: Preliminary studies. In Wattenberg L, Lipkin M, Boone CW, Kelloff G (eds): "Cancer Chemoprevention." Boca Raton: CRC Press, Inc., 1992, pp 165–180.
16. National Cancer Advisory Board: "Cancer at a Crossroads: A Report to Congress for the Nation." Executive Summary. pp 1–34, 1994.