Immunological Control of Virus-associated Tumors in Man: 
A Perspective¹

Paul H. Levine

Viral Leukemia and Lymphoma Branch, National Cancer Institute, NIH, Bethesda, Maryland 20014

The purpose of this Symposium has been to review the state of the art in 4 virus-associated tumor systems, i.e., lymphoma, leukemia, breast cancer, and cervical cancer, with the intention of identifying those aspects that are most applicable to current clinical problems. Following each session, the discussion leaders presented an overview of the problems peculiar to their disease area, which was based on the material included in the Symposium papers (3, 11, 15, 16, 22). Since logistic considerations have prevented us from including all of the papers presented at the meeting as well as many of the discussion points, this perspective will attempt to supplement the individual summaries by including additional pertinent material presented during the Symposium.

As might have been expected, EBV² required primary attention in this meeting because it is the only virus that has been shown to be pathogenic for man, oncogenic for primates, and readily identified in human tumors. As noted by Epstein (6), it has taken a decade to bring us from detection of the virus to consideration of a vaccine, and the lessons learned from research involving EBV and related lymphotropic herpesvirus may be applicable to studies in other virus-tumor systems as well.

While prevention continues to be a major goal of the field of viral oncolgy, a preventive vaccine for BL or any other human tumor does not appear to be on the immediate horizon for a number of reasons. As already stated (6), BL would be the most logical tumor to attack with a viral vaccine, but in this disease there is the problem of inoculating many normal individuals with potentially hazardous material in order to prevent tumors in a few. As Holland (11) has observed in the case of acute leukemia, the declining mortality due to improved conventional therapy diminishes the potential benefit of even the most effective vaccine and BL, like acute leukemia, is exceedingly sensitive to chemotherapy. As discussed by Meyer and Ennis (17), the benefit/risk ratio is a critical issue when inoculation of a normal individual is concerned. Our knowledge is growing rapidly, however, and these authors prudently observe that close interaction between basic scientists and regulatory agencies must be maintained as developments continue to arise in the laboratory and clinic. Such communication may well avoid large efforts and expenditures in building models that prove to be inapplicable to human disease.

Cervical cancer and breast cancer, with their greater degrees of morbidity and mortality, could be considered better candidates for a preventive vaccine because of their greater impact on society. Unfortunately, the data linking HSV-2 to cervical cancer remain weak, and a human breast cancer virus has not yet been detected. In both of these diseases, moreover, onset in adulthood makes evaluation of a vaccine more difficult. Unlike vaccines for acute infectious disease, implementation and evaluation of clinical trials in diseases of long or uncertain incubation period must be undertaken with great care from the statistical viewpoint. Hoover’s review (13) of the problems encountered in trying to determine whether Bacillus Calmette-Guérin prevents childhood leukemia is worthy of study before a vaccine trial is undertaken in any human cancer, although one would assume that a prospective study would avoid many of the problems of a retrospective one.

In an interesting corollary to the question of preventive vaccines, Klein et al. (15) noted that an EBV vaccine for infectious mononucleosis might have been considered if EBV were not so closely linked to BL and nasopharyngeal carcinoma. Yet a vaccine has been suggested for genital herpes with the possible side benefit of controlling cervical cancer. (One rationale for viral vaccines has been a belief that the best way to prove that a virus causes a specific neoplasm is to vaccinate against the virus and see whether the cancer is prevented in the vaccines.) There are, of course, great differences between EBV and HSV-2, as well as their associated diseases, but these somewhat variant philosophies regarding vaccination are an example of the areas that need further discussion as additional experimental data are obtained.

Although we may never see effective preventive vaccines translated from animal leukemia and lymphoma to their human counterparts, a number of benefits can still accrue from the interesting studies reported at this meeting. Viral vaccines may have a role in the treatment of leukemia as was discussed by Hersh, who summarized and updated his initial studies in humans using Rauscher leukemia virus (9, 10). Hersh saw no clinical benefit in his patients, but his approach may be worth reconsidering should the new isolates from leukemic cells (7, 25) prove to be leukemogenic. Certainly, the need to evaluate the viral aspects of any leukemia treatment can be invaluable as the experience of Holland and Bekesi (1, 12) in the treatment of murine and human leukemia demonstrates. The information derived from their apparently successful pilot studies also may be

¹ Summary of the symposium "Immunological Control of Virus-associated Tumors in Man: Prospects and Problems," April 7 to 9, 1975, Bethesda, Md.
² The abbreviations used are: EBV, Epstein-Barr virus; BL, Burkitt's lymphoma; HSV-2, herpes simplex virus type 2.
important to those concentrating on antiviral treatment programs. The failure to control BL and nasopharyngeal carcinoma with antibody and transfer factor directed against EBV may be explained by the need to deal with tumor antigens as well as viral antigens in the control of neoplastic disease, as discussed earlier in the symposium (1, 15).

One of the more promising areas related to control of virus-associated human tumors is the use of immunological tools for early diagnosis and monitoring of treatment. In experimental models for 3 of the human tumors discussed, lymphoma, leukemia, and breast cancer, it was noted that viremia and/or antigenemia preceded and predicted the subsequent onset of cancer in a reliable fashion (1, 8, 23, 26). Identification of relevant antigens, antibodies, and/or immune complexes has already been used in human cancer and, as far as virus-associated tumors are concerned, the EBV system has had particularly promising results. In cervical cancer, the discussants noted the possibility that immunological measurements of HSV-2 could be useful in clinical studies even in the absence of a proven etiological association. A number of HSV-2-related antigens have now been purified, and the reagents and technology are available to determine their role, if any, in the clinic. It is unlikely that serological assays will replace the Papanicolaou smear in the realm of early diagnosis, but measurements of immunity to purified tumor-related herpes antigens may assist in detecting early relapse in patients previously diagnosed.

An important aspect of each session was the consideration of appropriate animal models for problems in disease control. The heterogeneity in human leukemia noted by Holland (11) is more than matched by the variety of murine leukemias, and Jasmin’s review (14) of some of the principles involved in selecting the appropriate model systems were useful. In breast cancer, there was general agreement that the mouse provided a reasonable model for human breast cancer (4), but there is also heterogeneity in murine and human mammary cancer. Whether defined by relationship to menopause, by genetics, or by apparent mode of viral transmission, careful matching of the model system and clinical disease is very important. In view of the evidence for horizontal postweaning transmission of virus as well as perinatal transmission (2), a better understanding of the pathobiology in each mammary tumor virus model is needed before one selects the appropriate mouse model for the specific human entity. The finding in the mouse model of “private” antigens led to disappointing results in immunotherapy in contrast to the mouse leukemia and sarcoma systems (19, 20). While Simmons’ review (18) of his efforts in the treatment of murine mammary breast cancer pointed to a number of problems that must still be overcome if immunotherapy is to succeed, at least in the model systems, the improved reagents and techniques being developed in the course of these studies may be applicable to early diagnosis and the improved monitoring of conventional therapy.

The Marek’s disease system continues to provide an important model for human lymphoma in regard to pathogenesis as well as control. The important similarities between Marek’s disease virus and EBV in a natural setting have been reviewed (26), as have the opportunities for control (18), but the discussion also highlighted a number of important gaps that were not, to the best of our knowledge, being evaluated. Preliminary epidemiological and laboratory findings documented the importance of early infection, route of infection, genetic susceptibility, persistent viremia, viral strain differences, and blocking factors in the Marek’s disease virus system. Each of these aspects appear relevant to the etiology and monitoring of EBV-associated diseases, but much more information is needed. A nonscientific but very important concept that was raised was the need to broaden the research on Marek’s disease beyond the programs funded by federal agriculture programs. For obvious reasons, government-supported agricultural research in Great Britain and the United States has had to concentrate on controlling Marek’s disease rather than on studying it as a model for human lymphoma. Unless viral oncologists realize the importance of obtaining more information on the pathogenesis of Marek’s disease, increasingly successful control may lead to less support rather than more support.

Concern was expressed regarding the paucity of animal models for prevention and treatment of HSV-2-induced carcinomas, but in view of the uncertainty regarding the role of HSV-2 in cancer the continued emphasis on etiological studies as opposed to experimental models for disease control was reaffirmed.

The discussion on lymphomas included a review of the current status of studies on Hodgkin’s disease. Controversy continues regarding the transmissibility of Hodgkin’s disease (21, 24), although the effect of environment on this particular neoplasm (5) has not seriously been questioned. Since increasing doubt is placed on the role of EBV in Hodgkin’s disease, largely due to the absence of EBV genome in the cases studied thus far and the large number of EBV-seronegative Hodgkin’s disease patients, there is no clear path to follow with this tumor until a candidate agent is identified. In the discussion period, a parallel was drawn with feline leukemia, where the horizontal nature of disease transmission could not be delineated until the reagents to study feline leukemia virus became available (8).

In summary, the history of EBV research has demonstrated that the time required to be able to bring basic virological research to clinical application is quite long. The EBV-BL story has become a prototype for developing the current schema for demonstrating an etiological role for viruses in human tumors. The relationship between HSV-2 and cervical cancer has been investigated using methods proven in the EBV-BL studies. It is the failure to detect consistently HSV-2 genome in cervical cancer that has led to reservations regarding the role of this virus in the disease process and to the desire on the part of many investigators to look for other etiological agents. Since the application of research findings must be individualized on a disease basis, research workers should have the epidemiology, natural history, and available control measures in mind when attempting to develop model systems for the control of human cancer. As we have seen in this meeting, there are specific areas that require attention in each tumor system.

---

*R. L. Simmons and A. Rios. Active Specific Immunotherapy of Viral Associated Tumors: Animal Models – Mouse Mammary Carcinoma. Presented at this symposium but not published with these proceedings.*
discussed, and there are hopeful applications to diagnosis and/or treatment in each of these systems. Prevention remains an elusive goal not only because of the virological considerations discussed above but also because of the difficulties and dangers inherent in the design and implementation of a field trial. In only 1 instance, the improved survival of acute leukemia patients reported by Holland and Bekesi (12), have the results of studies in tumor-virus model systems been successfully translated to humans. Perhaps the next symposium will be able to provide additional examples of the successful translation of experimental data to the cancer clinic.

REFERENCES

Immunological Control of Virus-associated Tumors in Man: A Perspective

Paul H. Levine


Access the most recent version of this article at: [http://cancerres.aacrjournals.org/content/36/2_Part_2/867.citation](http://cancerres.aacrjournals.org/content/36/2_Part_2/867.citation)