In the current issue of ONCOLOGY, Drs. Emens and Jaffee have provided an excellent overview of the basic mechanisms involved in the tumor-specific immune response, as well as a comprehensive update of research on immune-based therapies for breast cancer. Over the past decade, several advances in basic immunology have resulted in a renewed interest in the development of cancer vaccines. First, as reviewed by Emens and Jaffee, we have a better understanding of how immunogenic proteins are recognized by the immune system, specifically by T cells. Second, it is now understood that a potentially therapeutic antitumor immune response must involve a variety of immune effectors, including both cytotoxic and T-helper cells. Furthermore, the importance of antibody immunity has been underscored by the clinical success with monoclonal antibodies such as trastuzumab (Herceptin). Finally, the development of powerful molecular tools has allowed the identification of multiple tumor antigens. Clearly human tumors are immunogenic. As this article emphasizes, the task before us now is to harness, augment, and manipulate the tumor-specific immune response for the benefit of cancer patients. Recently we have begun to see significant progress in the clinical application of cancer vaccines. Koutsiky and colleagues have elegantly demonstrated that immunization of young women with a vaccine targeting human papillomavirus (HPV)-16 protects not only against the development of HPV infection, but most likely against the development of cervical intraepithelial neoplasia. [1] Similarly, a large study from the Southwest Oncology Group demonstrated that patients with melanoma, whose disease has been completely resected and who have specific human leukocyte antigen (HLA)-immune phenotypes, can be immunized with a cell lysate-based vaccine resulting in a significant survival benefit. [2] Thus, cancer vaccines may have benefit not only in protecting from disease development in high-risk individuals but also in protecting against cancer relapse in the adjuvant setting. Breast Cancer Is Immunogenic

Breast cancer has not classically been considered an immunogenic tumor. Spontaneous regressions, however, have been reported in breast cancer patients, [3] and several investigators have demonstrated that breast tumors have lymphocytic infiltrates that may correlate with positive clinical responses. [4] These are the types of clinical observations that have been used to identify melanoma and renal cell carcinoma as cancers that may be amenable to immune-based therapies. The lack of investigation of the immunologic characteristics of breast cancer (until recently) most likely lay in the difficulty of documenting tumor antigen-specific immune responses in patients. For many years, a hallmark of defining a tumor as immunogenic has been the ability to generate cytotoxic T lymphocytes specific for autologous tumor and demonstrate cytotoxic T-cell activity in vitro. Propagating primary autologous breast cancer tumors in vitro is technically difficult. Furthermore, many primary breast tumors are small and pathologists often require the entire specimen for diagnosis and staging, leaving little material available for research purposes. Despite the difficulties in developing experimental systems, over the past decade, both genomic and proteomic techniques have resulted in the identification of dozens of immunogenic proteins that are expressed in breast cancer. Emens and Jaffee’s Table 1 lists a few of the most commonly studied breast cancer antigens. Role of Vaccines in the Treatment of Breast Cancer

As the authors note, vaccines targeting breast cancer antigens are being studied in minimal residual disease states. By evaluating active immunization in patients with functioning immune systems and without the multiple immunosuppressive effects of bulky disease, breast cancer vaccines are showing significant immunologic activity. Several of the studies outlined in the article demonstrate that the majority of patients can be immunized against breast cancer antigens. An important mechanism for measuring these is the identification of cancer-specific immunity in vaccinated patients. This helps to determine the need for vaccinating in minimal disease states. The levels of T-cell immunity to a foreign infectious antigen generated after active immunization is significantly less than the level of T-cell immunity needed to combat an active infection. Vaccination is meant to boost immunity to a plateau level, at which point T cells can rapidly expand to therapeutic levels after exposure to the pathogen. Increasingly, cancer vaccine studies are being designed in a similar fashion to those of infectious vaccines. The first phase of study is to determine the immunogenicity of the vaccine approach, and the next phase is to determine whether a specific immune response can protect against disease. Clearly, breast cancer vaccines have demonstrated preliminary success in the first phase of testing. Evolution of Combination Therapies

If breast cancer vaccines are to succeed in preventing relapse—a major clinical problem at many stages of breast cancer—then the clinical application of vaccines must be well integrated into adjuvant treatment. Emens and Jaffee describe the challenges in such integration. It has long been assumed that chemotherapy functions as a direct immunosuppressant. Recent data, however, suggest that vaccinating patients during recovery from induced lymphopenia may actually augment immune responses. [5] Therefore, there may be a strong rationale for developing vaccine programs intimately integrated with the use of chemotherapy, as described by the authors. Furthermore, combination immunotherapy may augment levels of immunity achieved after vaccination. Published data have demonstrated that cytotoxic T cells specific for HER2 have augmented lytic activity when breast tumor target cells have been preincubated with trastuzumab. [6] These early preclinical data suggest that combination therapies may enhance tumor-specific immunity rather than interfere with vaccination. Conclusions

In summary, there has been substantial progress in the development of immune-based therapies for breast cancer. It is now well established that breast cancer is an immunogenic tumor. Furthermore, dozens of breast cancer antigens have been identified. As outlined by Emens and Jaffee, several vaccine strategies targeting breast cancer have resulted in the generation of tumor-specific immune responses in patients with the disease. Clinicians are evaluating the application of breast cancer vaccines in the setting of minimal residual disease rather than in patients with advanced-stage refractory tumors. Improved clinical application has lead to successful trials of the evaluation of immunogenicity. Finally, the integration of breast cancer vaccines in the adjuvant setting may result in improved immunogenicity. The field is poised to focus on the next phase of breast cancer vaccine testing—determining clinical efficacy.

LEISHA A. EMENS, MD, PhD and ELIZABETH M. JAFFEE, MD