Summary

The fourth Expedition Inspiration conference was held March 21–23, 2000. While there are other conferences that concentrate on a particular facet of breast cancer, the design and goals of this conference are unusual. In order to maximize interaction of investigators and clinicians the meetings are small, invited, and private. The participants include both senior and junior physicians and scientists involved in clinical and basic research as well as clinical practice. The meetings serve four purposes: (i) Active discussion among participants who do not usually interact, (ii) Develop consensus as to the state of our knowledge as well as an action plan to stimulate future studies, (iii) Develop collaborative projects among the meeting participants, (iv) Foster new investigations by participants as well as others. This year immunology and the role of lymph nodes in breast cancer were the subject of the discussion. Investigators studying breast cancer biology, tumor immunity, potential cancer vaccines, and immunotherapy discussed potential therapeutic manipulation of the immune response to alter the natural history of breast cancer. Regional lymph nodes, the site of the immune response, are often affected early in the spread of breast cancer. For clinicians this involvement is central to planning effective treatment. The paradox that despite the involvement of these lymph nodes in mounting an immune response they are frequently the first site of breast cancer spread stimulated a great deal of discussion and some potentially interesting studies. The following consensus statement is the product of those discussions.

Lymph node and systemic metastases are probably distinct biological events

Long-term clinical studies of the natural history of breast cancer reveal that although the risk of distant metastasis increases with increased lymph node involvement the correlation is far from satisfactory. Approximately 25% of patients without disease in the axillary lymph nodes at diagnosis will develop distant metastases in their lifetime. There are several possible explanations for this observation:

1. The axillary dissection does not accurately detect all nodal disease. The tumor cells in those node negative women who develop distant metastasis could be different in phenotype from those that invade. The requirements for growth in lymph node may be different from those at a distant site.

2. The microenvironment is different in axillary nodes and the various metastatic sites and there has to be a match between tumor cell characteristics and microenvironment, similar to the ‘seed and soil’ concept.

3. Residual micrometastasis remaining after primary therapy grow and progress changing their phenotype.

In patients with node-positive disease, particularly if the tumors are small, a significant proportion will not develop metastatic disease. Thus, although the tumor cells in these node-positive patients acquired the characteristics of invasion, followed by growth in
lymph nodes they have not acquired the molecular characteristics necessary to grow at distant sites. 

**Action item:** Molecular analysis may be useful in understanding this difference.

**With the advent of mammographic screening**

*breast cancers are detected at a smaller size with a much lower likelihood of involved axillary nodes*

With the widespread utilization of screening mammography the majority of breast cancers now seen in the United States are less than 2 cm in diameter (T1). Mammography results in a 30% reduction in breast cancer deaths demonstrating that neither lead time nor length bias can explain the benefit. The resulting explanation for this is that waiting for clinical discovery of a palpable mass allows for 30% of the tumors to metastasize. Thus these small tumors appear to have less metastatic potential than do large tumors. This may be due to at least three not mutually exclusive mechanisms: fewer clonogens, tumor present for a shorter time resulting in less time for metastases, and less progression of the metastatic phenotype, that is, the malignant capacity of individual tumor cells continues to evolve or progress during its clinical sojourn. This is consistent with increasing histological grade as a function of tumor size as well as the increasing frequency of cancer related molecular abnormalities with tumor size. These progressive changes have been shown for p53, nm23, e-cadherin as well as an increasing microvessel density within tumors as they get bigger.

**Action items:** Determine why size determines the likelihood of axillary node involvement and survival.

Determine the molecular character of small versus large tumors and see whether this is evidence of tumor progression.

Determine whether involved internal mammary nodes have different molecular characteristics than axillary nodes.

Determine whether involved sentinel nodes – when they are the only involved nodes – differ molecularly from other involved axillary nodes.

**It is a paradox that tumor cells metastasize first to the regional lymph nodes where the principal cells of the immune response reside**

Does this occur because the lymph nodes serve in this situation simply as a passive sieve? Other possible reasons for regional lymph node metastases include: an antitumor immune response may not develop in a tumor-positive lymph node because of a lack of immune cells capable of recognizing the tumor antigens and generating a response; an absence or paucity of tumor antigens, or the immune system’s ignorance of their presence; insufficient stimulation by antigen-presenting dendritic cells or T-helper cells; or suppression or prevention of immune responses, possibly by the tumor cells themselves. Alternatively, antitumor immune responses may occur in the lymph node, but: the effector cells may be unable to make contact with the tumor cells to attack them; antigen-expressing tumor cells may be resistant to immune-mediated injury; the immune response may be a type (such as a non-toxic B-cell response) that is not capable of destroying the tumor cells; or the immune response may select for immunoresistant tumor cells. Another possibility is that an immune response capable of destroying tumor cells simply may not cope with the rapid growth of the tumor cells.

**Action items:** Rapidly progressing new laboratory techniques will help detect: immunologic features more likely to exist in *situ* in contrast to those conditioned by an ex vivo environment, genes activated in small numbers of cells selected from tissue biopsies, specific types of cells that contribute to immune responses, tumor antigens that are recognized by autologous T cells, and individual immune cells that recognize selected autologous tumor antigens.

Compare the immunological features of the following: Negative vs. positive lymph nodes; Peripheral blood lymphocytes vs. those in the regional lymph nodes vs. tumor infiltrating lymphocytes; Sentinel node lymphocytes vs. other nodal lymphocytes; Lymphocytes from grossly vs. microscopically involved sentinel nodes.

Determine the prognosis of isolated tumor cells in sentinel nodes.

There is no evidence of either a beneficial or harmful immunological response to breast cancer.

There is little evidence that the immune system has an effect on the natural history of breast cancer.

There have been only a few studies of the relationship between immune parameters in patients with breast cancer and prognosis or the natural history of the disease. Most of the studies that examined this important issue were performed more than 15 years ago, prior