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Alphavirus replicon particles containing the gene for HER2/*neu* inhibit breast cancer growth and tumorigenesis

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Abstract

Introduction Overexpression of the HER2/*neu* gene in breast cancer is associated with an increased incidence of metastatic disease and with a poor prognosis. Although passive immunotherapy with the humanized monoclonal antibody trastuzumab (Herceptin) has shown some effect, a vaccine capable of inducing T-cell and humoral immunity could be more effective.

Methods Virus-like replicon particles (VRP) of Venezuelan equine encephalitis virus containing the gene for HER2/*neu* (VRP-*neu*) were tested by an active immunotherapeutic approach in tumor prevention models and in a metastasis prevention model.

Results VRP-*neu* prevented or significantly inhibited the growth of HER2/*neu*-expressing murine breast cancer cells injected either into mammary tissue or intravenously. Vaccination with VRP-*neu* completely prevented tumor formation in and death of MMTV-c-*neu* transgenic mice, and resulted in high levels of *neu*-specific $CD8^+$ T lymphocytes and serum IgG.

Conclusion On the basis of these findings, clinical testing of this vaccine in patients with HER2/*neu*$^+$ breast cancer is warranted.

Keywords: adjuvant treatment, breast cancer, gene vaccines, immunotherapy, virus-like replicon particles

Introduction

The management of breast cancer currently relies on surgery, chemotherapy and radiotherapy. Despite recent advances in clinical management of breast cancer once metastasis has occurred, the probability of a complete cure is greatly reduced. Of the women who have no detectable lymph node metastases at the time of diagnosis, up to one-third later develop metastases [1]. In patients with metastatic disease that does not respond to radiotherapy or chemotherapy, immunotherapy may offer an additional form of cancer control [2-4]. Clinical trials of trastuzumab, a monoclonal antibody specific for HER2/*neu*, have demonstrated the utility of an immunologic approach for breast cancers that overexpress this gene [5-7]. A drawback to 'passive' immunotherapy using monoclonal antibodies is that the effect is short-lived. An alternative approach is active vaccination that could induce *neu*-specific cytotoxic T cells with the ability to control the growth of the primary tumor and metastases. However, unlike passive immunotherapy whose effectiveness quickly wanes, effector and memory T cells induced by vaccination may remain present and be able to respond to any metastatic cells expressing HER2/*neu* that arise after treatment.

HER2/*neu* is an excellent target for gene vaccines, and several preclinical studies have shown the effectiveness of plasmid vaccines encoding *neu* in murine models [8-16]. Using a plasmid markedly different from those previously described [8-16], we created an effective gene vaccine against HER2/*neu* [17]. The previously described ELVIS plasmid vaccine construct for HER2/*neu* contained the cDNA of a replicon RNA from the Alphavirus Sindbis

BSA = bovine serum albumin; FACS = fluorescence-activated cell sorting; FCS = fetal calf serum; FITC = fluorescein isothiocyanate; HA = hemagglutinin; IFN = interferon; IU = infectious units; MEM = modified Eagle's medium; MMTV = mouse mammary tumor virus; PBS = phosphate-buffered saline; VEE = Venezuelan equine encephalitis virus; VRP = virus-like replicon particles.