Overcoming Cancer Immune Tolerance and Escape

Commentary on Seavey et al., p. 924

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Although HER2/neu–targeted cancer vaccines have shown initial promise in the adjuvant setting, a therapeutic vaccine remains elusive due to the tumor escape mechanisms of established cancer. As described by Seavey et al. in this issue of CCR, a Listeria-delivered vaccine may help overcome immune tolerance, leading to an effective therapeutic vaccine.

In this issue of CCR, Seavey et al. (1) have reported the results of a novel HER2/neu cancer vaccine using a Listeria monocytogenes vector in a breast cancer murine model.

Since the inception of the theory of immunosurveillance in cancer in 1957, scientists have worked to develop effective immune-based anticancer therapies (2). Successful therapies such as trastuzumab (Herceptin) for breast cancer and cytokine therapy for renal cell carcinoma and melanoma have validated the field of immunotherapy in oncology. Using the body’s own adaptive immune system to identify and destroy cancer through vaccination is a logical next step for cancer immunotherapy.

The identification of many potential vaccine targets, tumor-associated antigens (TAA), expressed by a variety of cancers over the past 20 years, has led to an explosion of preclinical and clinical vaccine studies. Preclinical work has shown that TAA-primed lymphocytes are effective at identifying and destroying cancer cells; however, this work has not yet translated into an effective cancer vaccine in humans.

Like most novel oncologic therapies, cancer vaccines were first tried in patients with large-volume, metastatic disease with poor prognoses and limited remaining therapeutic options, with largely disappointing results. It is now evident that the immune tolerance, tumor suppression, and tumor escape mechanisms of established solid tumors are perhaps too great for the body to overcome and may never be effectively treated with monoimmunotherapy. In contrast, vaccinations in the adjuvant setting in patients who are clinically disease-free have shown encouraging initial results, and efforts continue to validate these vaccines for ultimate inclusion in standard treatment algorithms.

An area of intense research remains the use of therapeutic vaccines in metastatic cancer patients with low tumor burdens or minimal residual disease after resection. In this setting, a variety of techniques are being investigated to overcome immune tolerance and circumvent tumor escape mechanisms. These strategies include the alteration of naturally occurring peptides to increase immunogenicity, the use of novel immunoadjuvants, CTLA-4 blockade, T-regulatory cell depletion, and the use of a unique delivery system (1, 3–5). One promising method of vaccine delivery is presented by Seavey and colleagues in this issue of CCR—the use of L. monocytogenes as a vaccine vector.

Listeria is an attractive vaccine vector for many reasons. First, as a live bacterium, it is inherently capable of stimulating strong innate and adaptive immune responses without immunoadjuvants. Listeria, as a pathogen, also has a unique life cycle allowing it to live in both the phagosomal and cytoplasmic compartments of host cells, which enables the cell to process and present bacterial antigens on both MHC class I and II molecules. Additionally, Listeria is a well-studied bacterium with the complete genome sequence available; immunologic properties well studied; and established, effective culture and genetic manipulation techniques. Finally, Listeria produces listeriolysin O (LLO), a cytotoxic hemolysin protein, which is rapidly processed and cleared by cellular machinery and may lead to more rapid presentation TAAs when the latter are fused with LLO (see Fig. 1; refs. 6, 7).

Listeria vaccine vectors expressing LLO fused to influenza neucleoprotein have been used previously with success in murine models treating melanoma and colon cancer lines expressing neucleoprotein (8). The work by Seavey et al. in this issue of CCR advances this research by using the Listeria vector to treat cancers expressing a well-studied TAA, HER2/neu.

In their study, Seavey et al. use four different HER2/neu fragment:LLO fusion proteins—two extracellular HER2/neu protein fragments, an intracellular HER2/neu protein fragment, and a chimera protein containing dominant epitopes from the intracellular and extracellular portions of HER2/neu fused to LLO. In several well-designed experiments, the authors show that (a) the Listeria vectors express and secrete the desired HER-2/neu protein fragments; (b) the mouse splenocytes, which react to epitopes contained in the HER2/neu fragments secreted, are increased after inoculation with the vaccine; (c) the vaccines (including the chimera construct) have an anticancer effect in two different mouse tumor models, including mice genetically engineered to express the rat neu molecule, demonstrating at least some ability for the vaccine to overcome immune tolerance mechanisms; and (d) the Listeria vaccine expressing the LLO:HER2/neu chimera prevents or delays tumor metastasis in a lung seeding model. The
effectiveness of the LLO:HER2/neu chimera construct may expand the effectiveness of the vaccine by broadening the number of epitopes to which the immune system is primed with a single vaccine. With copious immunologic and corresponding mouse clinical data, the authors deliver compelling data that warrant further research.

HER2/neu is the most studied TAA in breast cancer. It is expressed by the majority of breast cancer cells, overexpressed in 20% to 25% of breast cancers, and expressed in many other epithelial-derived cancers. Overexpression of HER2/neu in breast cancer is associated with aggressive disease with a worse prognosis. Multiple immunogenic epitopes from the intracellular and extracellular regions of HER2/neu have been identified (9). The success of trastuzamab (Herceptin) is at least in part due to HER2/neu–specific immunologic mechanisms. Several previous phase I and II cancer vaccine trials have established naturally occurring and vaccine-induced HER2/neu immunity (10). All of these features make this TAA an attractive target for cancer vaccines, and, currently, there are over 20 phase I and II trials under way for HER2/neu–targeted vaccine therapies. Although some adjuvant vaccines are entering phase III trials, an effective HER2/neu–targeted therapeutic vaccine remains elusive. A direct comparison of immunologic and/or animal model effectiveness between the featured Listeria vector vaccination strategy and other HER2/neu vaccines already in human trials may elucidate the potential advantages of a Listeria–delivered vaccine.

Currently, Listeria as a vaccine vector is undergoing early human trials; however, there remain significant hurdles to the development of a Listeria-based vaccine therapy that is exportable to the community. Wild-type L. monocytogenes is a ubiquitous food-borne pathogen with increased virulence in immunocompromised individuals, including individuals undergoing chemotherapy. Because of the recognized attributes of Listeria as a vaccine vector, there has been much recent research into techniques to attenuate virulence of Listeria (11). These techniques include genetic alteration of virulence genes, growth factors, or their activators; development of conditionally lethal mutants that are dependent on exogenously supplied essential metabolites; and inactivation, particularly killed but metabolically active strains that are live bacteria unable to replicate due to cross-linked DNA. However, the ability of the bacteria to effectively stimulate the innate and adaptive immune system to the degree needed to overcome the cancer immune escape mechanisms may be attenuated along with the pathogenicity. Additionally, hurdles related to vaccine production that follow good manufacturing processes, storage, regulation, toxicology, and cost must be overcome before it can be applied therapeutically (12).

Harnessing the body’s immune system against cancer through vaccines is promising in theory and preclinical studies.  

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1 Available at http://clinicaltrials.gov.
Whereas multiple HER2/neu vaccine clinical trials are under way, most of the early success has been in the adjuvant setting. For therapeutic vaccines, the immune tolerance and tumor escape mechanisms of established cancers have proven to be complex and difficult to overcome. Although researchers seem to be tantalizingly close to developing effective therapies, no one has yet been able to definitively tip the scale against established cancers with vaccine immunotherapy. Seavey et al. have brought the *Listeria* vaccine vector technique closer to human trials by proving its effect against TAAs, including its ability to overcome immune tolerance, in animal studies. Although obstacles remain, further studies with *Listeria* vector vaccination techniques will advance our understanding of cancer immunology and hopefully lead to novel and effective immunotherapies.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**References**


