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## Immunotherapy: A Future Treatment Modality for Breast Cancer?

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Despite significant improvements in its diagnosis and treatment, breast cancer is still one of the leading causes of cancer death worldwide, with more than 500,000 women succumbing to this disease annually.<sup>1</sup>

Novel treatments are necessary to improve survival of patients. Currently, the mainstay of systemic modalities for treatment of breast cancer includes conventional cytotoxic chemotherapy, biologic treatments, and endocrine therapy for appropriate patients. Recently palbociclib, a targeted agent inhibiting cyclin-dependent kinase was approved by the Food and Drug Administration (FDA) for use in advanced estrogen receptor positive breast cancer patients in combination with exemestane, an aromatase inhibitor. Exploring new pathways and innovative approaches remain essential in cancer treatment research.<sup>2</sup>

Cancer immunotherapy including cancer vaccine development has been an area of active research for many years. It has long been known that body's immune system does not recognize tumor-associated antigens (TAAs) as foreign and develops tolerance towards them. Breaking this anergy may be an effective strategy to combat cancer. However, overcoming the complex immune escaping mechanisms developed by cancer cells is challenging. TAAs are generally processed by

antigen-presenting cells (APCs) and presented to T-cells through major histocompatibility complex (MHC). Through several mechanisms including expression of immunosuppressive molecules in tumor environment and tumor cells, cancer cells find a way to evade the immune system surveillance.<sup>3,4</sup>

Therapeutic cancer vaccines are developed to break tolerance to TAAs and to activate cytotoxic and helper T cells against tumor cells. How is this mission accomplished? Understanding the complex immunomodulatory and immunosuppressive mechanisms through which tumor cells grow, invade and metastasize is the key information. The next step would be to select the best targets for the development of cancer vaccines. An ideal TAA to serve as a target for a cancer vaccine should be highly immunogenic and oncogenic. Most TAAs are expressed in normal tissue; but, are overexpressed on tumor cells or are genetically mutated or epigenetically modified. Several TAAs have been identified in breast cancer, among which are human epithelial growth factor receptor 2 (HER2), mucin-1 (MUC-1), carcinoembryonic antigen (CEA) and human telomerase reverse transcriptase (hTERT). Several carbohydrate antigens like sialyl-Tn (STn) have been studied as potential targets.<sup>5</sup> The third step would be to find ways to promote the immune response to the vaccine. Several different strategies in cancer vaccine development have been employed to enhance the efficacy of vaccines. Co-stimulatory molecules and adjuvant compounds have been added to vaccine formulations to elicit a better immune response. Nanoparticle delivery systems and liposomal preparations are other examples of new technologies in cancer vaccine development to enhance efficacy.<sup>6,7</sup> There are various types of therapeutic cancer vaccines. The main categories

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include: peptide-based vaccines, dendritic-cell (DC) based vaccines, whole cell-based vaccines, and vector-based vaccines.

Peptide-based vaccines use antigenic epitopes of TAAs as their targets and are HLA-restricted to certain HLA types. The first peptide vaccines which were developed aimed at eliciting CD8 cytotoxic T cell response. Now these vaccines are generally manufactured to stimulate both cytotoxic (CD8) and helper (CD4) T cell responses. Peptides given alone are weakly immunogenic. Hence, several techniques were employed to enhance the binding affinity of MHC molecules to antigen epitopes and to increase their immunogenicity. Peptide-based vaccines are usually given with immunologic adjuvants or cytokines such as GM-CSF or IL-12 to increase recruitment of immune effectors. The benefit of peptide vaccines are their relatively low cost of production, ease of use and very limited toxicity profile. However, since they are HLA restricted, the population who may benefit from these vaccines is limited to that specific HLA type.<sup>8,9</sup>

Vector-based vaccines are made by transferring TAAs DNA sequences to a vector, which is usually a virus. Viral vectors can be genetically modified to harbor not only TAAs but also costimulatory molecules for a more robust immune response. Viral vectors are either replication-competent or replication-incompetent in human cells. Sometimes a prime and boost strategy using a replication-competent vector followed by replication-incompetent vaccine is utilized to generate a stronger and more sustained response.<sup>10</sup>

DC-based vaccines constitute another type of cancer vaccines. DCs are the most potent APCs and can activate both CD8+ and CD4+ T-cells. The benefit of this type of vaccines is that they can stimulate both class I and class II responses and can be modified to express different TAAs and co-stimulatory molecules. These vaccines are generally autologous and prepared from patient's own DCs. They can be pulsed by peptides, messenger RNA (mRNA) or be transfected by viral vectors to express various TAA or co-stimulatory molecules. Their disadvantage is their cost and labor-intensive production. To collect DCs, patients need to undergo leukapheresis which is a lengthy process. Then mononuclear cells will be cultured for several days and manipulated before the vaccine is ready for infusion. Sipuleucel-T is the first therapeutic vaccine which was approved for metastatic castration resistant prostate cancer in 2010. DC-based vaccines remain a focus of intense research in various kinds of cancers.<sup>11-13</sup>

Whole cell-based vaccines are either autologous or allogeneic. Autologous whole tumor cells vaccines use patient's own tumor cells to generate immunological response. Autologous whole tumor cell vaccines are less likely to miss any

unidentified antigens, but are expensive and their production is laborious. Obtaining significant amounts of tissue is not always feasible or easy. Also, since not all the immunogenic antigens in the autologous tumor cells are identified, the standardization of these vaccines and measuring the immune response poses another challenge. Allogeneic whole tumor-cell vaccines use different tumor cell lines and their preparation is easier, cheaper and faster. Whole tumor-cell vaccines are rendered replication-defective usually by irradiation. To enhance their efficacy, they can also be combined by different adjuvants or could be genetically modified to produce co-stimulatory molecules or cytokines.<sup>14</sup>

Several vaccines targeting different breast cancer TAAs are in pipeline at different stages of development. Unfortunately, none of them have yet been proven to have a significant clinical benefit. One reason that these trials have not been very successful may be high tumor burden and immune unresponsiveness in heavily pretreated patients. Moving vaccine trials to earlier stages of cancer treatment when there is minimal residual disease and when patient's immune response can be more effectively stimulated may render the vaccines more effective. Another consideration is that current criteria for tumor response and clinical benefit, which are based on reduction of tumor size and progression free survival, may not be optimal to measure immune responses. Immune system may take longer to kick in and patients may be taken off the trials before they have a chance to show a response. As demonstrated in sipuleucel-T phase III trial, this vaccine prolonged overall survival without significant effect on progression free survival or serum PSA.<sup>15</sup>

In conclusion, development of therapeutic cancer vaccines in breast cancer is currently a very active area of research. Better technologies and more appropriate end points and settings are needed to demonstrate the clinical benefit of cancer vaccines.

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