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Vaccine Development to Avoid Breast Cancer

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Abstract – Cancer vaccines have been fraught with many failures but have had a few recent successes. In order for this research to remain viable, major progress must be made to improve clinical outcomes in cancer immunotherapy. While there are no clear winners among the various strategies outlined, multiple approaches may be needed to provide a breast cancer vaccine to the majority of women due to differences in immunologic compatibility. The ultimate goal of breast cancer vaccines should be to reduce the risk of recurrence from minimally residual disease in patients with no evidence of disease following or in combination with endocrine therapy, chemotherapy, radiotherapy, and novel immunomodulators. While breast cancer vaccines may provide additional palliative benefits to patients with metastatic disease, this approach will likely need to be combined with chemotherapy and immunomodulators to improve outcomes significantly. Proper clinical trial design geared specifically toward cancer immunotherapy with rigorous immune monitoring methods and appropriate endpoints is essential in developing novel breast cancer vaccines. With intense collaboration, we may someday be able to stimulate the immune system's response to target specific cells as a means to cure breast cancer with improved precision, less toxicity to healthy cells, and minimal side effects. Years of unsuccessful attempts at fighting established tumors with vaccines have taught us all that they are only able to truly impact patient survival when used in a preventive setting, as would normally be the case for traditional vaccines against infectious diseases. A combination of immunopreventive cancer strategies and recently approved checkpoint inhibitors is a further promise of forthcoming successful cancer disease control, but prevention will require a considerable reduction of currently reported toxicities. These considerations summed with the increased understanding of tumor antigens allow space for an optimistic view of the future.

Keywords: Cancer Vaccines, Successes, Immunotherapy, Disease, Breast Cancer, Healthy Cells, Side Effects, etc.

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INTRODUCTION

The manipulation of the immune system through the administration of a vaccine to direct an effective and long-lasting immune response against breast cancer (BC) cells is an attractive strategy. Vaccines would have several theoretical advantages over standard therapies, including low toxicities, high specificity, and long-lasting efficacy due to the establishment of immunological memory. This reflects the intrinsic difficulty in breaking the complex immune-escaping mechanisms developed by cancer cells. New vaccines should be able to elicit complex immunologic response involving multiple immune effectors such as cytotoxic and antibody-secreting B cells, innate immunity effectors, and memory cells. Moreover, especially in patients with large tumor burdens and metastatic disease, combining vaccines with other strategies, such as systemic BC therapies, passive immunotherapy, or immunomodulatory agents could increase the effectiveness of each approach. We report results of most recent trials investigating active immunotherapy in BC and provide possible future perspectives in this field of research.

Each year, breast cancer accounts for more than 400.000 new cancer cases and more than 130.000 cancer deaths in Europe. Prognosis of non-metastatic breast cancer patients is directly related to extend of the disease, mainly nodal spreading and tumor size, and to molecular profile, particularly HER2 overexpression. In patients with HER2-overexpressing tumors, different studies have shown cellular and/or humoral immune responses against HER2 associated with a lower tumor development at early stages of the disease. These findings have so led to the hypothesis that the generation of an anti-HER2 immune response should protect patients from HER2-overexpressing tumor growth. Taken together with the clinical efficiency of Trastuzumab-based anti-HER2 passive immunotherapy these observations allowed to envisage various vaccinal strategies against HER2. The induction of a stable and strong immunity by cancer vaccines is expected to lead to establishment of immune memory, thereby preventing tumor recurrence. However, an immunological tolerance against HER2 antigen exists representing a barrier to effective vaccination against this on coprotein. As a consequence, the current challenge

for vaccines is to find the best conditions to break this immunological tolerance. In this review, we will discuss the different anti-HER2 vaccine strategies currently developed; considering the strategies having reached the clinical phases as well as those still in preclinical development. The used antigen can be either composed of tumoral allogenic cells or autologous cells or specific of HER2. It can be delivered by dendritic cells or in a DNA, peptidic or proteic form. Another area of the research concerns the use of anti-idiotypic antibodies mimicking HER.

Treating cancer with vaccines has been a challenging field of investigation since the 1950s. Over the years, the lack of effective active immunotherapies has led to the development of numerous novel strategies. However, the use of therapeutic cancer vaccines may be on the verge of becoming an effective modality. Recent phase II/III clinical trials have achieved hopeful results in terms of overall survival. Yet despite these encouraging successes, in general, very little is known about the basic immunological mechanisms involved in vaccine immunotherapy. Gaining a better understanding of the mechanisms that govern the specific immune responses (i.e., cytotoxic T lymphocytes, CD4 T helper cells, T regulatory cells, cells of innate immunity, tumor escape mechanisms) elicited by each of the various vaccine platforms should be a concern of cancer vaccine clinical trials, along with clinical benefits. This review focuses on current strategies employed by recent clinical trials of therapeutic cancer vaccines and analyzes them both clinically and immunologically (Holmes, et. al., 2008).

Recently, advances in early diagnosis and more effective treatments have reduced the mortality rate due to breast cancer (BC). However, despite this progress, BC remains a leading cause of death in the female population worldwide. In this scenario, manipulating the immune system to direct an effective and long-term immune response against BC cells through the administration of a vaccine is an attractive strategy. Tumor vaccination would have several theoretical advantages over standard therapies. First, the ideal tumor vaccine would induce potent and durable immune reactions against a broad spectrum of tumor antigens. It could be easily administered and manufactured, with modest side effects typical of conventional chemotherapies. Moreover, it would prevent further tumor recurrences, due to the establishment of persistent immune memory. At present, however, active immunotherapeutic strategies against cancer have failed to fulfill the above expectations in clinical trials (Viehl, et. al., 2005). This reflects the intrinsic difficulty in finding optimal targets for a cancer vaccine, the most effective type of vaccination, route of administration, and the most immunologically favorable setting of disease (eg, low tumor burden, not heavily pretreated patients). Most importantly, it reflects the difficulty in breaking the complex immune-escaping mechanisms developed by cancer cells. The aim of this review is to summarize recent advances in BC active immunotherapy, to address recent results from clinical trials, and to provide possible future perspectives in this field of research.

Cancer is the second leading cause of death in the United States, exceeded only by heart disease (23.1% versus 26.0% of total deaths, resp.). Currently, 1 in 4 deaths in the United States is due to cancer. According to American Cancer Society statistics, an estimated 1,479,350 new cases and 562,340 deaths from cancer are expected during 2009, with a slightly higher incidence and death rate in the male population. Prostate, lung, and colorectal cancers are the most common types of cancer in men; breast, lung, and colorectal cancers are most common among women. Altogether, lung, breast, prostate, and colorectal cancers account for 49% of cancer-related deaths in the U.S. population. Overall, except for lung cancer in women, incidence and mortality rates have steadily decreased for all 4 types of cancer in both men and women, probably due to both an increase in early diagnosis and improvements in therapy and combination therapies (surgery, radiotherapy, chemotherapy, and, lately, targeted therapy) (Czerniecki, et. al., 2007). But despite these encouraging advances, cancer is still a major public health problem worldwide, requiring new strategies and treatment modalities to optimize patient outcomes.

REVIEW OF LITERATURE:

Cancer is a hyper-proliferative disorder that involves morphological cellular transformation, deregulation of apoptosis, uncontrolled cellular proliferation, invasion, angiogenesis, metastasis and avoidance of immune surveillance.

Previous studies (from the National Centre Of Applied Human Genetics, School of Life Sciences Jawaharlal Nehru University) to understand the genotypic and expression status of genes involved in the DNA repair, immune surveillance and apoptotic pathways in sporadic breast cancer patients and the influence of somatic and germ-line mutations in mitochondrial genes / whole genome paved the way for the design of this study A series of genetic changes, each conferring a type of growth benefit, lead to progressive conversion of normal human cells into tumor cells, a process comparable to Darwinian evolution. With an estimated mutation rate of approximately 1 in 2 x 107 bases per cell division, while attaining 1014 target cells on an average in human with an abundant range of genes regulating all aspects of cell expansion, it is amazing that cancers arise in only 1 in 3 lifetimes.

These genetic abnormalities often create altered self-antigens in cancer cells, many of which have been shown to be recognized by the immune system eliciting tumor immune-surveillance mechanism. The

average adult human body generates approximately 60 billion cells per day, and as a consequence an equal number of cells must die by apoptosis to maintain cell homeostasis.

The rarity of cancer highlights the efficiency of potent antitumorigenic mechanisms presiding over somatic cells. Cancers dominate only when these mechanisms of DNA damage repair, immune surveillance and apoptosis have failed. Genetic susceptibility of host and environmental factors interact to influence carcinogenesis. Additionally, heterogeneity and adaptability are cardinal features of cancer (Czerniecki, et. al., 2007). At molecular level, it is likely that no two cancers are identical. Various forms of genetic and epigenetic changes, such as mutations, loss of heterozygosity (LOH), change in expression of microRNA, methylation along with global transcriptome changes, lead to aberrant pathway activation, cellular dysfunction and consequently premalignant epithelial changes.

Breast Cancer and its incidence: The incidence rate of 37.4 per 100,000 makes breast cancer the most common malignancy among women worldwide. It is considered to be the second leading cause of cancer death in women in developed countries. The estimated annual incidence of breast cancer worldwide is about one million cases (with ~200,000 cases in United States and ~320,000 cases in Europe).

The international agency of cancer research (IARC) had predicted an alarming increase in the incidence rate by the year 2010, mainly due to steadily aging population, growing adaptation of unhealthy lifestyles and the current trends in smoking prevalence (Pal and Mittal 2004), which is turning out to be true. Apart from the economic development, it seems genetic differences among populations and/or differences in lifestyle, including diet and environmental exposures play important role in differential incidence rates around the world (Jacob, et. al., 2007).

Further, an increase in the incidence of breast cancer when people migrate from low incidence to high incidence area suggests the involvement of complicated interaction between genetic and environmental factors in affecting the incidence rates.

India is a developing country with diverse population groups following variable lifestyles and dietary habits in the world. The incidence of breast cancer in India is significantly lower, almost one quarter to one-third of that in North America and Europe, respectively (GLOBOCAN 2002). This is primarily because of virtually nonexistent breast cancer screening programs, lack of awareness and socio-cultural attitudes, in some states of the country.

Reports from national cancer registries reveal breast cancer as the commonest cancer amongst women in major metropolitan cities of India with projected breast cancer cases in India to surpass cervical cancer in the year 2020. This increasing rate of Breast cancer in India demands for a quick study of the disease and search for markers and effective therapy.

Types of breast cancer: The majority of the breast cancers are classified into one of the following categories, infiltrating ductal carcinoma, infiltrating lobular carcinoma, ductal carcinoma in situ, lobular carcinoma in situ, inflammatory carcinoma, Paget's disease and cystosarcomaphyllodes (Aurisicchio, et. al., 2009). There are other tumors of the breast, such as angiosarcoma, squamous cell cancer and lymphoma, which are quite rare.

a. **Infiltrating ductal carcinoma:** It is the most common type of invasive breast cancer comprising about 65-85% of all cases. It starts in the cells that line the milk ducts in the breast, grows outside the ducts, and often spreads to the lymph nodes. On a mammography, it is usually visualized as a mass with fine spikes radiating from the edges and/or small micro calcification with a group of small white irregular dots. On physical examination, this lump usually feels much harder or firmer than the benign breast lumps in the breast. On microscopic examination, the cancerous cells invade and replace the surrounding normal tissue inside the breast.

b. **Infiltrating lobular carcinoma**: It is a type of cancer that accounts for 5-10% of breast cancers. A cancer of lobular origin that invades and grows into the surrounding tissue but on examination of the breast there is usually not a hard mass, but rather a vague thickening of the breast tissue, often difficult to differentiate from infiltrating ductal carcinoma on mammography. Lobular carcinoma can occur in more than one site in the breast (as a multicentrictumor) or in both breasts at the same time (as bilateral lobular carcinoma).

c. **Ductal carcinoma in situ (DCIS):** In this type of breast cancer, cells are completely contained within the breast ducts and have not spread into the surrounding breast tissue. DCIS may also be referred to as noninvasive or intraductal cancer. Most women with DCIS have no signs or symptoms so it is mostly found through breast screening. The DCIS usually shows up in the mammogram as an area in which calcium has been deposited in the milk ducts (known as micro calcification).

A small number of women with DCIS may have symptoms such as a breast lump or discharge from the nipple. DCIS is frequently multifocal, i.e., it is located in more than one area of the breast.

d. **Lobular carcinoma in situ (LCIS):** It is an early type of breast cancer that develops within the milk-producing glands (lobules) of the breast and does not penetrate through the wall of the lobules; most cases of lobular carcinoma in situ do not progress to invasive lobular cancer. However, having this type of cancer places a woman at increased risk of developing an invasive breast cancer later in life (Radkevich-Brown, et. al., 2009). There are no signs or symptoms ordinarily associated with LCIS such as lumps or even abnormalities on a mammogram. The only way LCIS can be diagnosed is through a breast biopsy. The risk of developing an invasive cancer of the breast with LCIS is approximately 1% per year.

e. **Inflammatory carcinoma:** This is a sub-type of infiltrating ductal carcinoma, but named for its typical clinical presentation. It causes edema, hyperemia, tenderness and rapid enlargement of the breast. Blockage of the lymph channels due to a rapid growth of the cancer in the breast tissue usually causes the reddened appearance, causing it to swell and appear infected. In 90% of the cases at the time of diagnosis, the cancer has already spread to the lymph nodes.

f. **Paget's disease:** This disease described by Sir James Paget, an English surgeon in 1874, accounts for about 1-4% of all the breast cancers. It typically results when malignant cells that originated in the ducts of the mammary glands spread to the epithelium. In Paget's disease, the nipple and areola (the area surrounding the nipple) are typically red, inflamed and itchy. The nipple may be inverted (turned inwards) and there may be a discharge from the nipple. It can be mistaken for a benign skin condition unless there is a high index of suspicion.

g. **Cystosarcomaphyllodes:** This cancer is very different when compared with other cancers of the breast. It is a type of tumor found in breast tissue. It is often large and bulky and grows quickly. It is usually benign but may be malignant. Also called as phyllodestumor. It seldom spreads to the lymph nodes, but can metastasize to other parts of the body through bloodstream.

Targets and strategies of BC vaccines: It has been well established that the immune system plays a role in controlling tumor growth, and adaptive immunity is the main mediator of "spontaneous" regression of certain types of cancers (Mittendorf, et. al., 2008). The immune system has the ability to recognize several types of antigens expressed on tumor cell surfaces, namely the tumor-associated antigens (TAAs). TAAs are presented to immune system effectors such as T-cells by the tumor itself, through the major histocompatibility complex (MHC) or, more likely, by antigen presenting cells (APCs), in particular macrophages and dendritic cells (DCs). These cells are essential in processing antigens into immunogenic peptides and presenting them to naive T-cells through the MHC complex. Through a complex and regulated system of co-activator and inhibitory molecules expressed on the cell surface, these cells play an essential role in priming T lymphocytes and activating an immunogenic response against specific targets. The presence of tumor-infiltrating lymphocytes has been correlated with better prognosis in several types of cancers. However, tumor cells often develop the ability to circumvent the surveillance of the immune system. In the tumor microenvironment, molecules such as vascular endothelial growth factor, transforming growth factor (TGF)-β, and interleukins are abundant and both actively down regulate the immune function and promote tumor progression, invasion, and metastasis. In addition, tumor cells can directly down regulate T-cell function through expression of trans membrane inhibitory molecules such as FasL or B7-H1/PD-L1 or, indirectly, by promoting functionally suppressive CD4+FoxP3+ T lymphocyte (TReg) function. Finally, cancer cells can modulate expression or mask TAAs, reducing their availability and presentation to immune effectors. All these mechanisms can therefore lead to altered DC and T-cell function, and, as final result, to impaired immune response against tumor cells. Immune-escaping mechanisms are particularly active in epithelial cancers such as BC. However, some degree of immune response against TAAs can be demonstrated in BC patients (Benavides, et. al., 2009). This has prompted researchers to develop active immunotherapies to therapeutically amplify these weak responses against known immunogenic BC antigens. In fact, the aim of an effective therapeutic vaccine is to break peripheral tolerance and activate low-affinity T-cells that were not eliminated during selection in thymus. Among them, human epithelial growth factor receptor 2 (HER2), carbohydrate antigens, telomerase reverse transcriptase (HTERT), and mucin-1 (MUC-1) have received the greatest attention for vaccine formulations (Jacob, et. al., 2009) and have been tested in clinical trials. In order to produce an effective vaccine, an antigen or a pool of antigens (as for whole-tumor-cell vaccines) should be delivered through an appropriate formulation. Activation of the immune system could be enhanced by including adjuvant compounds, and appropriate monitoring

techniques should be prompted to assess the immunologic response (Lekka, et. al., 2010).

Peptide-based vaccination: Peptide-based vaccines aim at inducing immune responses (including antibodies, cytotoxic T lymphocytes [CTLs], and helper T-cells) using antigenic epitopes derived from TAAs. Many of the first cancer vaccine strategies focused on inducing tumor-specific CD8+ cells with MHC class I restricted short peptides. It is now clear that these CD8+ T-cell responses are typically weak and short-lived. Further studies have clarified that triggering the CD4+ T-cell response is critical for maximizing tumor immunity, as it both optimizes the CD8+ T-cell response and supports the humoral antitumor immune response. Thus, researchers have focused on studying peptide-based vaccines that are able to trigger both CD4+ and CD8+ responses, using longer peptides or mixtures of epitopes. Peptide vaccines have several potential advantages, which include easy manufacturing, easily evaluable immunological response, and low expected toxicities. These advantages have made the peptide-based vaccination widely studied and employed in clinical trials. However, this strategy presents some objective limitations. First, to be effective, peptide vaccines often require co-administration of an immunological adjuvant. Adjuvants play an important role in favoring recruitment and efficient stimulation of immune effectors. Identification of an even more efficient adjuvant for a given vaccine is crucial for the effectiveness of the formulation and has been the object of intense research. Second, most of the peptide-based vaccines tested are restricted to HLA-A2. This limits the number of potentially benefiting patients (Kageyama, et. al., (2008). Third, although easily monitored, immune response is directed against one or a few epitopes, possibly reducing the effectiveness of response and favoring mechanisms of immune escape. Finally, we should consider population- and patient-specific variability in antigen processing and presentation, which could affect the effectiveness of such a strategy.

DNA-based vaccination: The principle of this approach is based on the assumption that the DNA encoding for a given TAA can be taken by APCs, translated into protein, and finally processed for presentation. DNA can be delivered naked or complexed with other molecules. Frequently, the most used vectors are viruses that are able to efficiently transfect target cells. Recently, new technologies such as nanoparticles and liposome preparations have been successfully employed to deliver DNA vaccines. A large body of evidence supports the idea that stimulating a coordinated immune response, involving cellular, humoral, and innate immune effectors (natural killer cells and macrophages), most effectively mediates tumor rejection. DNA vaccines, because of their unique mechanisms of action, could stimulate a more “physiologic” immune response against antigens and could be produced on a larger scale. However, finding an effective vector can be challenging.

Dendritic cells-based vaccination: DCs are the most important APCs. They naturally express high levels of MHC molecules, co-stimulatory proteins, and cytokines. Autologous DCs can be modified by fusion with cancer cells by pulsing with peptides or by transfection to express tumor antigens. DC vaccination represents one of the most intriguing platforms in cancer vaccines. In fact, DCs are able to stimulate both class I and class II responses and can be further modified in order to co-express co-stimulatory molecules, and responses can be directed against multiple targets. This type of platform has been successfully employed and approved for clinical use in castration-resistant prostate cancer. However, this vaccine platform remains technically challenging due to the uncertainty related to the optimal route of administration and expansion, maturation, and/or activation of DC cells, which is not easily achievable ex vivo and, as a result, this limits larger scale manufacturing.

Whole cells-based vaccination: Another potential approach is immunizing the patient with whole tumor cells, derived from the patient herself (autologous) or from cell-line cultures (allogeneic). These vaccines have been shown to induce antigen-specific T-cell responses. However, more frequently, tumor cells act as antigenic pool for in vivo or ex vivo APCs presentation. To enhance immunological response, tumor cells can be genetically modified to express co-stimulatory molecules or cytokines. Theoretical advantages of such approach comprise providing a pool of tumor antigens, generating immune responses to more than one antigen, and thereby possibly overcoming the tumor antigen loss. Moreover, this could lead to a more “complex” response, involving both CD4+ and CD8+ T-cells, against different antigens. Potential drawbacks may be the triggering of autoimmunity and difficulties in monitoring the consequent immunologic response that may be directed against unknown TAAs.

Combining BC vaccines with other strategies: Despite the encouraging preliminary results and excellent profile of tolerability, BC vaccines still show limited clinical efficacy. Antigen variability and mechanisms of tumor immune-escaping can impair the effectiveness of active immunization. Moreover, possible difficulties of the immune effectors to reach poorly vascularized tumors and high tumor burdens may contribute to limit the efficiency of vaccines. For patients with larger burdens of tumor and disseminated disease, it is fairly clear that vaccines alone are not able to outmatch the immune tolerance mechanisms of cancer cells; moreover, these become progressively more complex with tumor progression. Thus, a possible way to overcome the known limits of

active immunotherapy may be combining BC vaccines with other strategies, such as systemic BC therapies, passive immunotherapy, or immunomodulatory agents. Interaction of BC vaccines and systemic therapy could be complex and poorly predictable. Thus, any combinatorial strategy requires strong biologic rationale. For example, target-immune checkpoints and reducing activity of T-Regs could overcome immune tolerance and increase the effectiveness of vaccination. Especially for patients with advanced disease, incorporating drugs that target BC-biology-inhibiting key intracellular signaling pathway may be required to enhance the activity of vaccines. In this field, results of first pivotal studies incorporating BC vaccines with targeted therapies have already been reported. Finally, disruption of tumor cells by conventional therapies could lead to the release of tumor fragments/antigens that are otherwise not accessible for presentation and processing and proinflammatory cytokines, with the final result of an increased immune response.

CONCLUSION:

Cancer vaccines are developed to specifically target only tumor cells while preserving normal tissues from a non-specific toxicity. So far the data from clinical trials have shown that cancer vaccines induce low toxicity. This represents a major advantage over conventional therapies such as chemotherapy or radiotherapy. Particularly, the potential risk of developing an auto-immune disease using cancer vaccines has not been reported in clinical trials conducted so far. However, Jacob *et al.,* have shown that tumor regression in mice following anti-HER2 DNA vaccination and Treg depletion can exacerbate autoimmunity, which warrants close monitoring during immunotherapy trials. Indeed, it must be kept in mind that the risk of cardiotoxicity related to treatment with trastuzumab of patients with HER2-positive breast cancer is real but low. If the risk linked to the use of vaccines were in the same range of magnitude (very low percentage of patients), the current data from vaccine clinical trials would not be able to bring it to light due to the limited number of enrolled subjects. In addition, anti-HER2 vaccines present the potential disadvantage that in the case of interruption of the vaccination scheme due to important toxicity linked to the HER2 targeting, these effects would persist, whereas trastuzumab cardiotoxicity is generally reversible at the end of administrations of the Ab. Performing extensive clinical toxicology and preclinical studies remains thus essential.

Although anti-HER2 vaccines can induce a specific immune response, the clinical benefits observed remain questionable. Several hypotheses have been proposed to explain these negative results: (i) deleterious impact on the immune system of treatments such as chemotherapy and radiotherapy prior to vaccination, (ii) the difficulty to break the immune tolerance against the HER2 antigen, (iii) the ability of tumors to escape the immune system and (iv) the too advanced stage of disease of patients chosen for immunization. On the other hand, it is also important to keep in mind that many vaccine trials have targeted populations of patients in the adjuvant setting, who have a minimal tumor mass, and in whom, as a consequence, it is more difficult to evaluate the extent of the clinical benefits of such a therapy.

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