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BREAST CANCER VACCINATION- AN ENVISIONED FUTURE

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ABSTRACT

It is possible to make breast cancer vaccine however using body's own immune system to cure this cancer. Preventing breast cancer in the manner we prevent early diseases as cholera, influenza and polio is the key investigation of today's work. Further prototypical strategies are presented for the development of prophylactic breast cancer vaccines. The main focus of this review is about various researches (2000-2014) and hypothesis for breast cancer vaccination which are on the main platform. To know various mechanism employed to treat breast cancer and if it is long living and effective or not. A virus, called HMTV or human mammary tumor virus, has been found in 40% of breast tumors. Thus if we know the causative agent, a vaccine is possible. Various researches used various proteins and virus plus prophylactic techniques to get a vaccination and remained successful or progressing towards it. This review article depicts all those mechanisms one by one. Similarly what future vision can be drawn using all the recent work on breast cancer vaccination?

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INTRODUCTION

How good it sounds if we tell our daughter breast cancer has gone forever. Breast cancer is the second most killing cancer in the world that covers not only women but also men and food animals. Many researches are being done in the world to make its vaccination as to prevent it before it comes. It is yet a challenge to scientists as the main causative agent involved is not known. The ultimate difficulty for prophylactic vaccination of cancer arises from the fact that tumor antigens are variations of self-proteins and there would be mediations of clear autoimmune complications if used in a preventive vaccine setting (2).

It is not confirm if a virus is involved in breast cancer to make a vaccine. This is because vaccines are developed when exact cause of a disease is known either virus, bacteria or protozoa.

HPV causes not only cervical tumors, but cancers of the head and neck, as well as the vulva, vagina, penis and anus. Hepatitis B can cause liver cancer, Gulley says. The Epstein-Barr virus can lead to at least three types of lymphomas.

Another virus, called HMTV, or human mammary tumor virus, has been found in 40% of breast tumors. HMTV seems particularly common in a rare but often deadly form of breast cancer, called inflammatory breast cancer, according to a 2010 study in Cancer(1). Similarly scientist are *unaware* if HMTV is the ultimate cause of killing breast cancer. Fran Visco, president of the National Breast Cancer Coalition says they do not want to creep in the case of breast cancer by holding themselves to medicines which is not a good ultimate hope. He is of the view that there must a better cure than treating patients with harsh chemotherapies and burning them out (1). Scientists are taking a related approach, testing treatment vaccines designed to prevent tumors from metastasizing or spreading to other tissues, a condition that is fatal.

Evidences for Breast Cancer Vaccine Research

Alpha- Lactalbumin based

Lactalbumin, alpha is a protein that in humans is encoded by the *LALBA* found in the milk of mammals and its expression is up regulated in response to the hormone prolactin thus increases the production of lactose(4). It is a multimer keeping affinity for calcium and zinc ions and thought to have antitumor activity. It is this thought that convinced Dr. Vincent Tuohy at the Cleveland Clinic to use this protein as a fighter for breast cancer in past child bearing premenopausal age(3). The research was done on mouse breast cancer models to form a prophylactic vaccination for humans in future. α -Lactalbumin was considered as the target autoantigen because it appears in high concentration in most breast carcinomas(3). It is expressed in mammary epithelial cells only during lactation thus this vaccine if emerged is used only in post lactating woman. Results said that immunoreactivity against this protein provided nominal safety and treatment in breast carcinomas of transgenic mouse models and against 4T1 transplantable breast tumors in BALB/c mice. It is safer of any inflammation in non-lactating women because the protein is conditionally expressed in lactation only. This research is further planned for human trials within 2 years (5) and the Cleveland clinic is gathering funds for this purpose.

The human trial phase I will include women with triple-negative breast cancer who have recovered from current standard of care involving chemotherapy, radiation therapy, and/or surgery (5). By this we will be able to know the frequency of dosing and the ultimate dosing to cure the disease with an optimum immune response. The second phase of the trial will involve the women with no breast carcinoma but are susceptible to breast tumor in future. These women will volunteer for bilateral mastectomy as a result lowering their risk factor of developing breast cancer. In the meantime this trial will help to determine the safety of vaccine in the absence of breasts tissues

Though α -lactalbumin vaccination delays and treats breast tumor growth yet a more advanced vaccine strategy which surpasses the condition of lactation is needed. However, as most breast cancer occurs in the late 35-50 years so we can say this would be a better option if no other solution is found.

Immune system diversion

On the other hand a research completed where an experimental breast cancer vaccine, developed by Dr. Leisha Emens at the Johns Hopkins Kimmel Cancer Center, is currently being tested in clinical trials(6). She struggles to train the immune system for combating metastatic breast cancer. Dendritic cells are used as the main target to get work from.

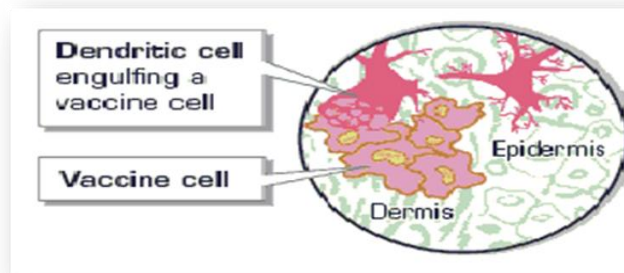
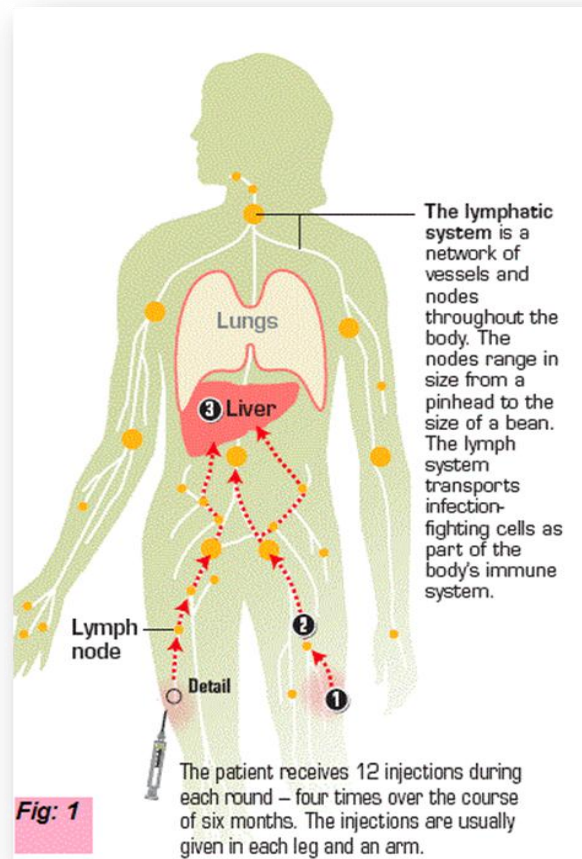


Figure 1: How metastatic breast cancer is controlled by vaccine using dendritic cells of the body as main worker

How this vaccine works is a simple mechanism as indicated in the figure points.

1. The vaccine is injected under the skin releasing GM-CSF (granulocyte-macrophage-colony stimulating factor) protein which alerts the body's immune system. Dendritic cells are attracted towards the vaccine and engulf vaccine cells.
2. Taking this information dendritic cells move towards the T-cells of the body in lymph nodes and train them to identify, approach and kill the breast cancer cells.
3. T-cells keep the memory of metastatic cell design in the other organs such as liver and get active to kill breast cancer cells in future attacks, that is a marvellous approach.

Dendritic cells are antigen-presenting cells, also known as *accessory cells* of the mammalian immune system. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system. They act as messengers between the innate and the adaptive immune systems. They are present in the skin and other organs exposed to the outer environment. Stimulating dendritic cells *in vivo* with microbial extracts causes the dendritic cells to rapidly begin producing IL-12.⁽⁷⁾ IL-12 is a signal that helps send naive CD4 T cells towards a Th1 phenotype. The final consequence is priming and activation of the immune system attacking against the antigens which the dendritic cell presents on its surface, our vaccine in breast cancer case.

Interesting thing is that Emen prepared this vaccine put it in liquid nitrogen till the patients take it but the vaccine was not enough to cure cancer cells. That is regulatory T-cells in the body were shielding the tumor cells. Thus chemotherapy in the form of

cyclophosphamide the day before taking vaccine was given along to knock down the regulatory T- cells (8). Dose of cyclophosphamide was kept 200 ug/m² as the higher dose may kill the vaccine taught cells (8). Doxorubicin and Herceptin (advance drug in breast cancer cure) was also given in any of two trial groups of females and mouse models. Results were acceptable with therapeutic outcomes and depend on choice of right medication with vaccine. Emen did many test to check if vaccine is really beneficent and how much including the sign that If the area around the test gets red and swollen, there has been an immune reaction (9). This research can be a great achievement if it works as it is designed, yet there might be short comings as dendritic cells if receive the right information or not. There are chances of autoimmune diseases and further studies would confirm this strategy in a better way. This could be a fastest approach as we are diverting the body's own defense system and strengthening it for better survival in breast cancer – a positive view.

STn-KLH cancer vaccine

This vaccine is also in its trial III stage and proposes therapy for metastatic breast cancer. Due to this vaccine a high antibody effect is produced against synthetic STn epitope and against a natural mucin, OSM by which STn- like epitopes are expressed. Theratope vaccine proved reduced metastatic breast cancer in a randomized study with pre-treatment of low dose cyclophosphamide. The anti-STn and anti-OSM antibody titers were higher in the patients who received cyclo intravenously before THERATOPE. The life span of the patient increased due to this combined treatment with IV cyclo as compared to patients with oral cyclo plus theratope or only theratope therapy (11). An inverse relation was found in anti STn titer and tumor growth and on the mean while no relation in anti KLH and tumor growth. Because of this significant result scientist proceeded further for phase III clinical trials of this vaccine.

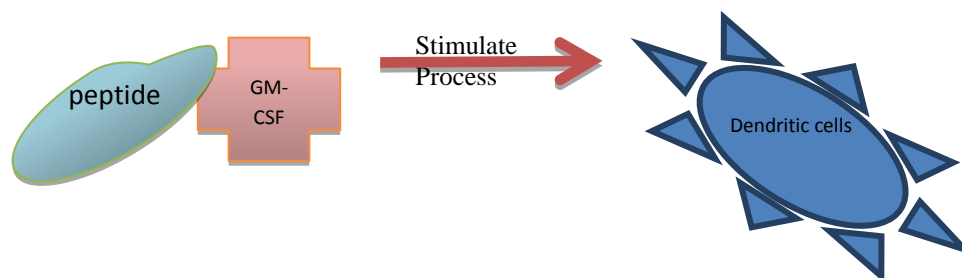
Poxvirus vaccine

According to a research smaller one, poxviral vaccine is effective to halt the metastatic breast cancer. Small research was done on 26 patients out of which one woman survived better with no breast cancer in x ray findings and now four years past she is living her life with no carcinoma of breast.

The vaccine is PANVAC vaccine in which two viral vectors--recombinant vaccinia and recombinant fowlpox--which are given sequentially (10). Both vectors contain transgenes for the tumor-associated antigens epithelial mucin 1 and carcinoembryonic antigen, which are altered or overexpressed in most carcinomas. The vectors also contain transgenes for three human T cell co stimulatory molecules required to enhance immune response: B7.1, intracellular adhesion molecule-1 and leukocyte function-associated antigen-3. PANVAC is injected subcutaneously and processed by the body's antigen-presenting cells. Early clinical trials are evaluating PANVAC alone and in combination with conventional chemotherapy and/or radiation. Thus this is a future promise to use this vaccine for the breast cancer safely. It is to be noted that PANVAC is a cancer vaccine that promise to cure breast cancer as well and not breast cancer specific.

Peptide Vaccine

This technique is used in MD Andersons Texas where protein is used to get vaccination goal. The tumor-associated antigen most frequently used in breast cancer vaccines is the HER2 oncoprotein, which favors the growth of tumor. Peptide vaccines are made by taking a small amino acid sequence (peptide) from a tumor-associated antigen (14). GM-CSF was used as immunoadjuvant that combines with peptide eliciting the body's immune response. Many cells are responsible for breast cancer, thus making vaccine for each cell target is necessary to stop metastasis. However, the peptide length gives idea of types of immune cells that stimulates. The peptide-GM-CSF combination stimulates the dendritic cells in injection site and processes them for a better immune response.



any HER2- derived vaccines are there effective 60% on low HER2 breast cancers (14). Similarly E75is one of HER2-derived peptide vaccine, a 9 amino acid peptide that combines with major histocompatibility complex MHC class 1 molecule thus stimulating CD8-positive T-cells, and these T-cells are so specialized that they eventually detect the foreign antigen and attack it. Further they release cytotoxic enzymes to kill them. The short coming is that these cells are only active on patients whose cells are positive for human leukocyte antigen (HLA)-A2 or HLA-A3. Just these HLA type cells will allow there surface to peptide for activating T-cells.

This vaccine has passed phase I-II trials and is now under phase III trial of its success which will enroll 700 breast cancer patients. The primary end point goal of study is 3 year survival free of ailment. GP2 and AE37 are the other peptide vaccines of same institution of which AE37 can present blood cells of all HLA types – promiscuous, and starts immune response as well.

Fos-related antigen 1

In this work published in 2003, DNA vaccine against murine transcription factor Fos-related antigen 1 gave breast cancer therapy in which oral DNA therapy reduced not only tumor growth but also pulmonary metastasis. This antigen factor is overexpressed in

aggressively proliferating D2F2 murine breast carcinoma. This oral DNA was carried by attenuated *Salmonella typhimurium*, encoding murine Fos-related antigen 1, fused with mutant polyubiquitin, and cotransformed with secretory murine IL-18 (12). 60% of vaccinated mice got tripled life span. Hence this vaccine gave protection for mice breast cancer growth as well as metastasis control using the tumor angiogenesis suppression mechanism. Also this vaccine needs to be tried for human to get further benefits. Hence no such approach is seen.

Endoglin (CD105), a co-receptor in the TGF-beta receptor complex, is over-expressed on proliferating endothelial cells in the breast tumor neovasculature and thus offers an attractive target for anti-angiogenic therapy (16). Oral DNA encoding murin endoglin found to be effective in controlling breast cancer through one of the study.

Legumain-based minigene vaccine

TAM (Tumor associated macrophages) is the important factors in tumor angiogenesis and metastasis. Inhibiting TAM inhibits tumor growth and dissemination. Legumain based minigene vaccine (13) proved helpful in mice model. CD8+ T- cell response is initiated that causes suppression of tumor in mice. The minigene vaccine responses similar to whole gene vaccine which provided better stage for future clinical trials in cancer prevention. The advantage is that we do not need to encode the whole gene as minigene works with same efficiency.

Arguments

Dendritic cell vaccine approach is attractive as from the history the only vaccine approved for cancer from U.S Food and Drug Administration is sipuleucel-T (Provenge), a dendritic cell vaccine used in men with metastatic hormone-refractory prostate cancer(14). This prove may take us to next level that dendritic cell may be helpful in making a long-term breast cancer vaccine. Some scientists say that the work of dr. Vincent to destroy the whole tumor by body's immune system is worthy as one must destroy the tumor not the organ (15). Other people say that a satisfactory result oriented work is still needed as all people who announce for vaccine do not have some real time invention. Yet positive argumentations reveal this work to be better and lifesaving. They say saving a life is better than saving an organ like breast. Similarly they hope that a time will come when vaccination for breast tumor will kill only tumor- **tumor specific force**.

We are at unprecedented level of breast cancer where most of the vaccines do not enter second or third stage of trial. The ultimate reasons of this may be lack of funds as many companies are promoting their cause by gathering funds. I am working on estrogen receptor sensitivity of body's immune sytem provided proper funding is arranged. Similarly the confidence on the vaccine is also a hinderance for further clinical trials. Most prominent reason is that breast cancer is a more complex disease than influenza or polio. The causative agent is not clear and uncontrolled proliferation of cells gives a clear target for man to oppose it. However, today we are at better position for curing breast cancer than past.

Recommendations

The benefit of the peptid vaccines is that they are inexpensive and convenient. On the other hand they are sometimes HLA specific e.g E75 vaccine. Also these vaccines are not effective in metastatic tumors because of their less potential to deal with bulky tumors said by the Dr. Mitendorf, Assistant professor in the department. Researches other than this are done in university of Pennsylvania, Leeds University, Hoffington, Oxford university and many other areas which are still out of the camera, proved useful in a way that a solution possibility can be envisioned in future. Combining all researches in a master brain and getting a life time solution to eradicate breast cancer is not just a dream now.

Cycline E and folate binding protein antigens may be targeted to get potential vaccines in the future making this promise stronger. A vaccine might be combined with a drug that inhibits CTLA-4 (14), a protein that downregulates T cells i-e Ipilimumab, an antibody that targets CTLA-4, might be appointed to get a huge immune system response.

Alpha-lactalbumin, peptide vaccine and other types using dendritic cells of body immune system can prove therapeutic features soon. The need of the day is to continue work on all the aspects. The final results lies in one of them yet one may be more or less potent than other.

Conclusion

This is real time task to know if such a vaccine can come which fights for all cell types of a breast cancer. Because vaccine like cholera, mumps, measles are prepared for specific type of calls but in breast cancer number of cell progenies participates. The nature of cancer to grow is really a question for scientists, as a cell becomes abnormal and grows generation over generation producing various types after each generation. In the meantime as many number of antigen types are emerging with the abnormal growth of cells. Second problem lies with metastatic nature of cells for which such vaccine is required that handle heavy cancer load on the body. Thus we can categorize our vaccine for metastatic breast cancer and non-metastatic one.

Legume based mingene vaccine in 2008 is a marvellous technique that sounds good in a scientific way. Hence the need of funding and serious clinical trial approach is needed. The fact that minigene is similar in potency than whole gene is of main interest. Also this technique controls both tumor growth and metastasis. But how much time it takes to do so in humans is a new area for research. Yet we are hopeful for what we have envisioned that breast cancer has ended. This is the promise of nature that there is a cure for every disease that makes my commitment powerful to eradicate breast cancer in near future using vaccination technique.

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