

Cancer Vaccines: The New Fight Against Cancer

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N S Vasanthi was until recently associated with the laboratory of Prof. Henrik Clausen, Faculty of Health Sciences, University of Copenhagen, Denmark working on a variety of projects in the field of glycobiology and immunology. During her stay at Denmark she was extensively involved in the design and production of mucin based cancer vaccine and development of assays for the detection and quantification of cancer associated glycoforms of mucins in serum.

Key words

Cancer, immunotherapy, therapeutic vaccine, prophylactic vaccine.

The inability of the body's immune system to differentiate cancer cells from normal cells allows cancer cells to proliferate in an uncontrolled manner. Newer strategies are being researched to overcome this immunological tolerance to cancer. Provoking the body's immune system to generate vaccines against cancer is emerging as an important type of immunotherapy to treat cancers. These cancer vaccines, which have fewer side effects, and offer great promise. Many such vaccines have been identified and several of them are under clinical trials currently.

The Problem of Cancer

In our body, cell division, differentiation and death are highly controlled mechanisms tightly regulated by tissue homeostasis. However, should a cell acquire certain kinds of genetic alterations, then it escapes out of this tight control, dividing uncontrollably. In this process, it accumulates further genetic alterations, which subsequently lead to tumor growth. These tumors are either cancerous (*malignant*) or non-cancerous (*benign*). Malignant tumours spread through the bloodstream and lymphatic system (*Figure 1*) and invade other parts of the body (*metastasis*). They also avoid natural cell death (*apoptosis*). The swollen veins around the surface of the malignant tumour appear like the legs of a crab. This appearance perhaps was responsible for the naming of the disease as 'cancer' which in Latin means 'crab'. The immune system that normally differentiates self from non-self, 'tolerates' the growing tumor because of its inability to detect the small differences in the abnormally growing cells. Thus, immunological tolerance allows cancers to multiply in the body.

The different types of cancers that occur in nearly every body



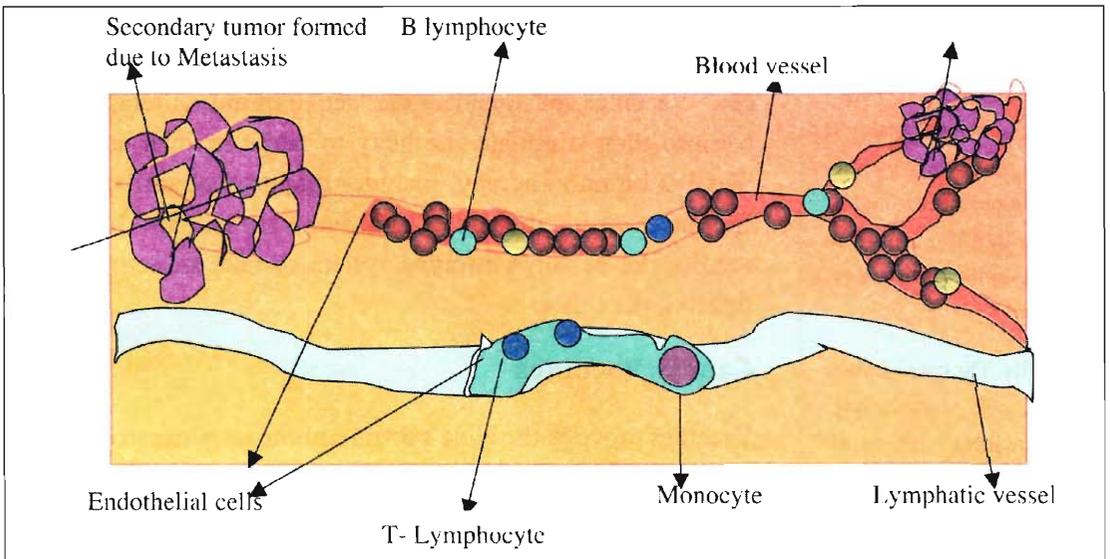


Figure 1. Metastasis of cancer by primary tumor cells penetrating blood vessels.

organ are grouped based on the types of tissue in which they originate. Carcinomas are cancers of the epithelial tissue (also called solid tumors), sarcomas are connective tissue associated cancers and leukemia and lymphoma are blood and lymph tissue associated tumors. Mixed types of cancers do not belong to any single category. Different kinds of cancers grow at different rates and respond very differently to treatments.

Methods of Cancer Treatment

Surgery, radiation therapy and chemotherapy are the three accepted, standard treatments for cancer. Surgery removes tumors and reduces tumor burden. Radiation therapy destroys cancer cells with high-energy ionizing radiation and thus kills residual tumor cells in the surgical field. Chemotherapy modifies or destroys cancer cells with drugs and kills both residual and micro-metastatic diseases systemically. ‘Immunotherapy’ is emerging as a fourth and still investigational type of therapy which is relatively a new addition to the family of cancer treatments. Sometimes it is also referred as biological therapy, biotherapy, or biological response modifier therapy.

Immunotherapy involves treatment by agents from biological sources that provoke the immunological response of the human

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Glossary

Homeostatis: Minor changes in individual cells and organs, which by summation perform complex, integrated functions to maintain the life of an organism.

T-cells: The type of white blood cell (lymphocyte) responsible for cell-mediated immunity

T-cell clones: Groups of cells that is descended from a genetically identical T-cell.

Adjuvants : An immunological agent that increases the antigenic response

Humoral side of the immune system: The body's immune system dominated by circulating Antibodies.

B-cells: The type of white blood cell (lymphocyte) that when stimulated by an antigen differentiates into plasma cells which synthesize the antibodies that circulate in the blood and react with the specific antigens.

body. The response is designed to repair, stimulate and/or enhance the immune system to directly or indirectly fight cancer. Vaccines are considered as 'active immunotherapy' agents because they stimulate the body to make its own antibodies. 'Passive immunotherapy' includes monoclonal antibodies that are made outside the body and given to the patient. It does not require the person's immune system to take an active role in fighting the cancer.

Cancer Vaccines

Vaccines provoke the body's own immune response to overcome the tolerance to cancer cells and thus to recognise and destroy them. They fight against the uncontrolled growth and spread of cancer cells without harming the healthy ones. They exhibit minimal toxicity, induce appropriate tumor-specific immune responses against both primary and metastatic lesions and stimulate a memory response to protect against tumor recurrence.

When cells mutate and start growing uncontrollably, markers called 'antigens' appear on the surface of cancer cell. Even though cancer cells are different from normal cells, the antigenic variations are very small and hence are unrecognized by the body's immune system. Thus, the body becomes tolerant to cancer cells allowing them to form tumors by multiplication. Immunological tolerance to cancer is achieved either by nondeletional or deletional mechanism. In the nondeletional mechanism, the number of T-cell clones in a given immune range that recognize tumor antigens is small. Hence, rapidly growing tumors escape body's immune response. Insufficient activation of stimuli and/or vigorous suppression of the antigen-reactive T-cell contribute to nondeletional method of tolerance. Deletional mechanism refers to the elimination of the antigen-reactive cells themselves. This occurs during the normal process of achieving self-tolerance as many tumors contain antigens that are found on at least some normal cells.

Cancer vaccines are designed in such a way that they typically



consist of a source of cancer-associated material, the antigen, along with other components as immune stimulators to provoke the body's immune response. Whole cells, proteins, or other materials are removed from cancer patients and are chemically modified or genetically modified by adding new genes or killed by radiation or treated with DNA containing instructions for making a particular antigen. Since the immune response produced by tumor antigens are generally weak, adjuvants like cytokine, BCG (the vaccine that protects against tuberculosis) or other compounds, that are already known to boost the immune system, are mixed with the antigen. When such a vaccine is injected into the patient, the immune system is activated to recognize cancer specific vaccines as foreign invaders and attack cells with similar antigens, without harming normal cells. Thus, the vaccine overcomes the immunological tolerance and induces the body's immunity to destroy cancer cells. This is diagrammatically described in *Figure 2*.

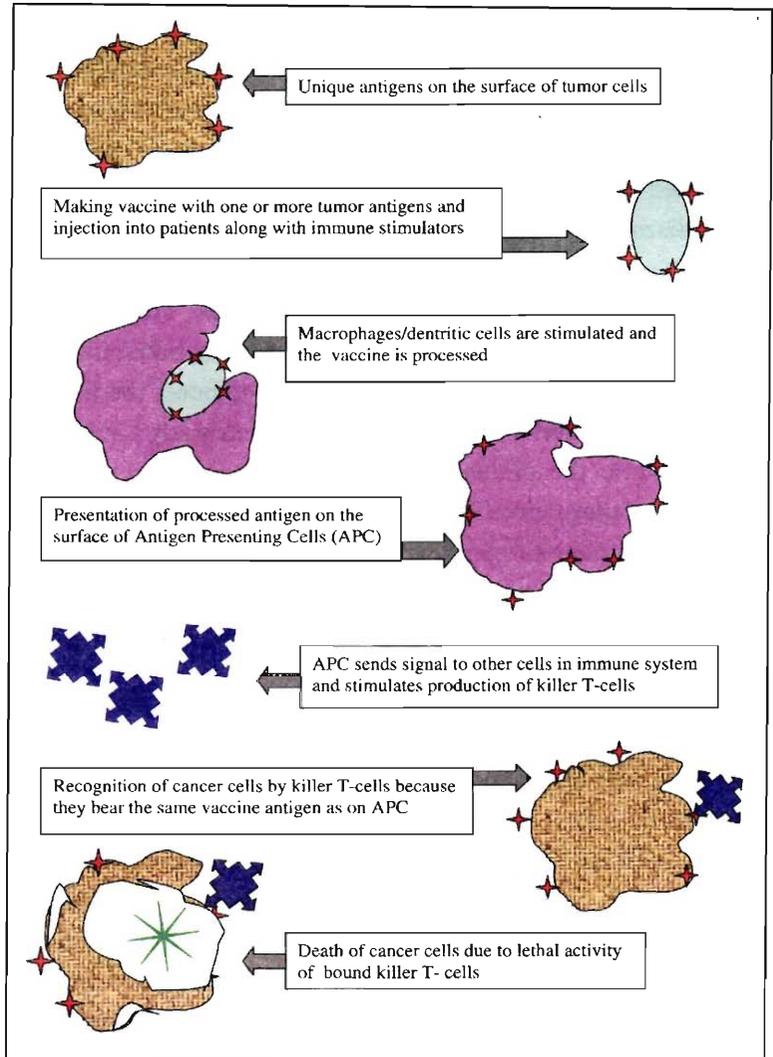
Cancer vaccines can either be 'general' displaying a protein that is commonly found in certain cancer or 'specific' and custom made from cancer cells of patients. The marker antigens of the cancer cells are identified, made in the laboratory and injected into patients to activate the immune response. The vaccine attracts immune cells such as dendritic cells and macrophages. These cells engulf the vaccine and present fragments of these antigens displayed on their own surfaces (antigen presenting cells) to other immune cells. Lymphocytes, including helper T-cells, killer T-cells and B-cells circulating in the blood stream all the time, are called into action. Since cancer cells also have the same antigen like the vaccine, killer T-cells activated by the vaccine, lock onto the cancer cells and shoot lethal holes in them causing cancer cells to burst and die. The surviving B- and T-cells develop into specialised 'memory cells' that remember to destroy the cancer cells when they arise the next time. In order to maintain the memory, booster injections of the vaccine are given periodically. In addition to the cellular side of the immune system described above, some cancer vaccines stimulate the

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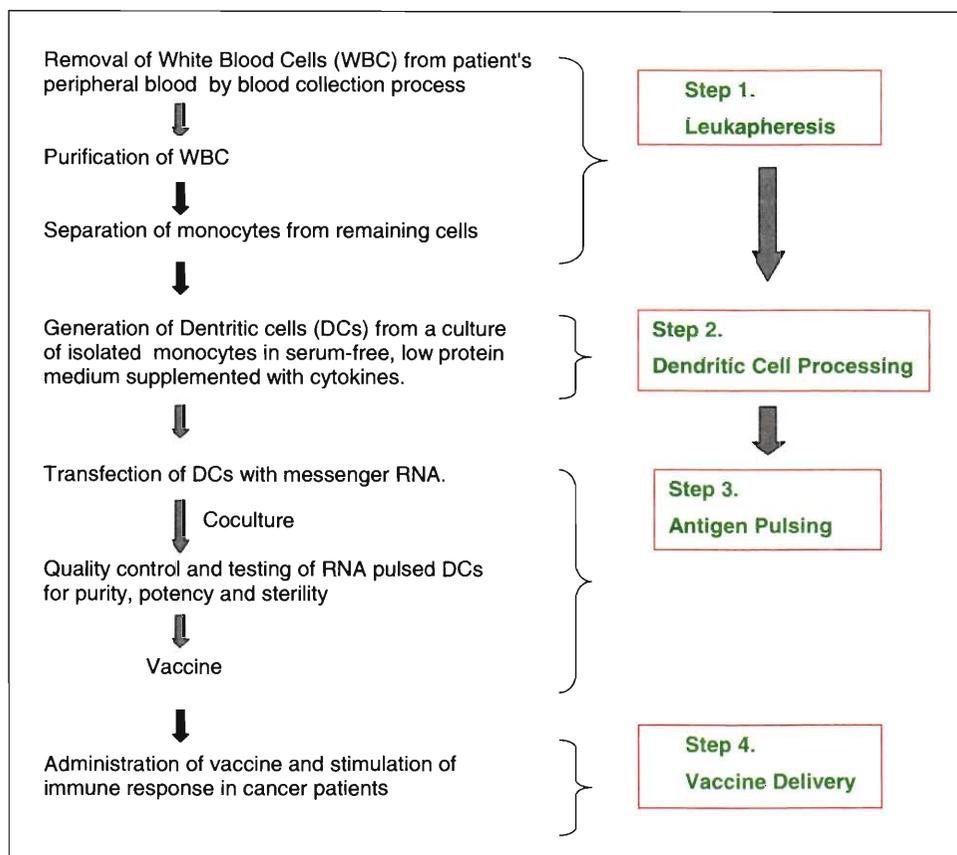


Figure 2. Eliciting immune response with vaccine for detection and elimination of cancer.



humoral side of the immune system wherein the antibodies are called into action. In this process, after vaccine injection, B-cells develop into 'plasma cells' and make antibodies which circulate in the blood, and remove the cancer antigens and stop metastasis. By the procedure above, vaccines are being developed either to treat existing cancer (*therapeutic vaccines*) or to prevent the development of cancer (*prophylactic vaccines*). Both the types of vaccines have the potential to reduce the burden of cancer. However, most of the cancer vaccines are envisioned to be administered after the onset or detection of disease and thus are therapeutic rather than prophylactic.





Cancer vaccines typically consist of a source of cancer-associated material such as cells, proteins or other materials from patient's own body, along with substances that increase the body's own immune response against the antigen. Antigen vaccines, anti-idiotype vaccines, dendritic cell vaccines, DNA vaccines, tumor cell vaccines, gene modified vaccines, etc., are the different devices used for presenting cancer antigens to the body's immune system. The challenge has been to find better antigens and also to pack the antigen in such a way to enhance the patient's immune system to fight cancer cells. Dendritic cells are specialized cells of immune system that initiate immune response by processing antigen and presenting it to lymphocytes to stimulate the production of more lymphocytes. *Figure 3* outlines the steps involved in the development of a dendritic cell vaccine from the white blood cells of a patient.

Figure 3. Development of dendritic cell based vaccine.

Suggested Reading

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The Future of Cancer Vaccines

It was in 1893 when the New York surgeon, William Coley, first recognised the possibility of developing cancer vaccines. He reported the regression of several human sarcomas following immune stimulation with a bacterial toxin. Since then, cancer vaccines have been researched and much has happened in the subsequent years. Animal based laboratory studies have shown promising results in which vaccines have successfully stimulated the immune system. Most of the research into vaccines have looked at cancer of prostate gland, breast, pancreas, colon and rectum, lung, skin (mainly malignant melanoma), kidney, ovary, bladder, cervix and to treat lymphoma and leukaemia. However till now, the Food and Drug Administration (FDA), USA has not approved any therapeutic vaccine for use as a standard treatment. This means that cancer vaccines are only available to those who enrol for clinical trials. Some of the cancer vaccines which are currently located in different phases of clinical tests are listed in *Table 1*.

A few prophylactic vaccines currently under investigation have the potential to reduce the risk of cancer. Non infectious components of cancer causing organisms serve as antigens for these vaccines. The most successful testing of a prophylactic cancer vaccine is hepatitis B vaccine which protects against liver cancer. The FDA has licensed the use of this vaccine against hepatitis B virus. Another example of a prophylactic vaccine is that against the human papilloma virus type 16 (HPV 16). HPV is a common infection in the general population, but some serotypes (HPV 16 and 18) are associated with cervical and other cancers. Therefore, a prophylactic vaccine against HPV 16 would attempt to protect against the infection that can lead to cancer.

Cancer vaccines offer therapeutic advantages over existing therapies by being associated with very few side effects thus enabling the patients to maintain a higher quality of life during the course of treatment. Since these vaccines exploit molecules that exist in the body they overcome problems associated with reaction to foreign entities.



Vaccine Name	Description of Vaccine	Effective against
Cancer VAX	Polyvalent protein from three melanoma cell lines	Melanoma
OncoVAX	Patient's tumor cell	Colorectal cancer
Onyvax	Monoclonal antibody 105AD7 anti-idiotypic vaccine	Colorectal adenocarcinoma
Onyvax-P	Three cell lines of different stages of the disease	Prostrate cancer
Oncophage®	Heat shock protein from individual patient's tumor	Melanoma; Pancreatic cancer; Renal cell cancer
RESAN	Imitators of 3 tumor antigens	Different malignant and benign tumors
Mylovenge®.	Dendritic cell	Myeloma
Melacine	Lysed cells from two human melanoma cell lines	Melanoma
ALVAC-CEA/B7.1	Deactivated strain of a virus	Colorectal cancer
VG-1000 Vaccine	Patient's plasma	Carcinomas; melanomas; some sarcomas and leukemia
GVAX	Modified cancer cell of patient	Lung cancer
AG-858	Heat shock protein	Myelogenous leukemia
NY-ESO-1 peptide vaccine	Cancer testis antigen (NY-ESO-1)	Sarcoma of soft tissues
Not named	Carcinoembryonic antigen	Gastrointestinal tract cancers
Not named	Patient's tumor cell	Adenocarcinoma of colon
Not named	Prostrate specific membrane antigen	Hormone-Refractory Prostate Cancer
Not named	Patient's dendrite cells, Patient's tumor cells and GM-CSF	Kidney cancer

Table 1. Select examples of cancer vaccines that are currently located in different phases of clinical trials.

The traditional standard methods are unable to solve the problems of metastases and relapses of malignant tumors. Use of vaccines in combination with surgical or other traditional treatment may form a rational approach in cancer treatments as it is expected to prevent relapses and to cure cancers completely. Furthermore, they can considerably prolong the lives of the terminal stage cancer patients which is not achieved by the traditional methods.

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