# EDITORIAL

## CANCER VACCINES

Vaccines are medicines that boost the immune system's natural ability to protect the body against "foreign invaders" that may cause disease. Vaccines are composed of a suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae), administered for the prevention, amelioration or treatment of infectious diseases.

Recently the role of vaccines has been expanded to develop a cancer vaccine that either prevents infections with cancer-causing viruses, or treat existing cancers.

Some cancers, such as cervical cancer and some liver cancers are caused by viruses, and traditional vaccines against those viruses, such as HPV vaccine and Hepatitis B vaccine, will prevent those cancers. This type of cancer vaccine is known as **preventive (or prophylactic) vaccine** [1]. Cancer preventive vaccines target infectious agents that cause or contribute to the development of cancer. They are similar to traditional vaccines, which help prevent infectious diseases such as measles or polio by protecting the body against infection. Both cancer preventive vaccines and traditional vaccines are based on antigens that are carried by the infectious agents and that are relatively easy for the immune system to recognize as foreign. It is believed that microbes cause or contribute to between 15 percent and 25 percent of all cancers diagnosed worldwide each year, with the percentages being lower in developed countries than in developing countries. The International Agency for Research on Cancer (IARC) has classified several microbes as carcinogenic (causing or contributing to the development of cancer in people), including HPV and HBV [2] (Table-1).

Apart from Hepatitis B vaccination, the US Food and Drug Administration (FDA) approved the vaccine known as Gardasil®, which protects against infection by two types HPV-specifically, types 16 and 18 – that cause approximately 70 percent of all cases of cervical cancer worldwide.

Treatment (or therapeutic) vaccines, are the other type of vaccine which are intended to treat already existing cancers. Some researchers believe that cancer cells routinely arise and are destroyed by the healthy immune system; cancer forms when the immune system fails to destroy them. They are separating proteins from cancer cells and immunizing cancer patients against those proteins, in the hope of stimulating an immune reaction that would kill the cancer cells. Active clinical trials of cancer treatment vaccines are under way in various centers, especially in the National Cancer Institute in United States of America (Table-2).

**Cancer treatment vaccines** seek to target an antigen specific to the tumour and distinct from self-proteins. Selection of the appropriate adjuvant, molecules that activate antigen-presenting cells to stimulate immune responses, is required; at the present time, only aluminum-based salts and a squalene-oli-water emulsion are approved worldwide for clinical use. The effective vaccine also should seek to provide long-term memory to prevent tumour recurrence. For total tumour elimination, both the innate and adaptive immune systems should be activated.

Tumour antigens have been divided into two broad categories: shared tumour antigens; and unique tumour antigens (Table-3). Shared antigens are expressed by many tumours. Unique tumour antigens result from mutations induced through physical or chemical carcinogens; they are therefore expressed only by individual tumors [3]. Vaccine containing whole tumour cells has been used but these have been less successful.

Antigens are often not enough to make effective cancer treatment vaccines. Reasearchers often add extra ingredients, known as **adjuvant,** to treatment vaccines. These substances serve to boost immune responses that have been set in motion by exposure to antigens or other means. Adjuvant used for cancer vaccines come from many different sources. Some microbes, such as the bacterium Bacillus Calmette-Guerin (BCG) originally used as a vaccine against tuberculosis, can serve as adjuvant especially for treatment of urinary bladder cancer [4].

Clinician can also use natural or synthetic **cytokines** as adjuvant. Cytokines are substances that are naturally produced by white blood cells to regulate and fine-tune immune responses. Some cytokines increase the activity of B cells and killer T cells, while other cytokines suppress the activities of these cells. Cytokines frequently used in cancer treatment vaccines or given with them

**Table-1: Microbiological Agents Known to Cause Cancer in Human Beings**

| Infectious Agents | Type of Organism | Associated Cancer(s) |
|---|---|---|
| Hepatitis B virus | Virus | Hepatocellular carcinoma |
| Hepatitis C virus | Virus | Hepatocellular carcinoma |
| Human papilloma virus | Virus | Cervical cancer |
| Epstein-Barr virus | Virus | Burkitt lymphoma, Hodgkin lymphoma, Nasopharyngeal carcinoma |
| Human T-cell lymphotrophic virus 1 | Virus | Acute T cell leukemia |
| Human Herpes 8 virus | Virus | Kaposi sarcoma |
| Helicobacter pylori | Bacterium | Stomach cancer, Gastric lymphoma |
| Schistosoma hematobium | Parasite | Urinary bladder cancer |
| Liver fluke (opisthorchis viverrini) | Parasite | Cholangiocarcinoma |

**Table-3: Various Tumour Antigens Being Used for Cancer Vaccines**

| Antigen | Type of Cancer |
|---|---|
| **Shared Tumour Antigens** | |
| Carcinoembryonic antigen | Colorectal cancer, stomach cancer, pancreatic cancer, breast cancer and non-small cell lung cancer |
| Cancer/testis antigens | Melanoma and cancers of the ovary, tongue, pharynx, brain, lung, colon and breast |
| Mucin-1 | Cancer of breast, prostate, colon, pancreatic and non-small cell lung cancer |
| Gangliosides | Melanoma, neuroblastoma, small cell lung cancer and soft tissue sarcoma |
| P53 protein | Many human cancers |
| HER2/neu protein | Breast, ovarian, and several other types of cancer |
| **Unique Tumour Antigen** | |
| Epidermal growth factor receptor | Glioblastoma |
| Melanoma differentiation antigens | Melanoma |

**Table-2: Active Clinical Trials of Cancer Treatment Vaccines by Type of Cancer**

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|---|
| Bladder cancer |
| Brain tumours |
| Breast cancer |
| Cervical cancer |
| Kidney cancer |
| Melanoma |
| Multiple myeloma |
| Leukemia |
| Lung cancer |
| Pancreatic cancer |
| Prostate cancer |
| Solid tumours |

include interleukin 2, interferon alpha, and granulocyte-macrophage colony-stimulating factor [5].

## PROBLEMS

A vaccine against a particular virus is relatively easy to create. The virus is foreign to the body, and therefore will express antigens the immune system can recognize. Furthermore, there are usually only a few viable variants of the virus in question. It is very hard to develop vaccines for viruses that mutate constantly such as influenza or HIV.

The cancer treatment vaccines have not been so successful so far. One of the reasons is that a tumour can have many different types of cells in it, each with different cell-surface antigens. Furthermore, those cells are derived from the individuals with cancer, and therefore display few if any antigens that are foreign to those individuals. This makes it difficult for the immune system to distinguish the cancer cells from normal cells [5].

## FUTURE COURSE

Several studies have suggested that cancer treatment vaccines may be most effective when given in combination with other forms of cancer therapy. In addition, in some clinical trials, cancer treatment vaccines have appeared to increase the effectiveness of other cancer therapies. Additional evidence suggests that surgical removal of large tumour masses may enhance the effectiveness of cancer treatment vaccines. In patients with extensive disease, the immune system may be overwhelmed by cancer and effective immune responses cannot be achieved. Surgical removal of the tumour may make it easier for the body to develop an immune response [6]. Glaxo Smith Kline (GSK) is testing its MAGE-3 vaccine in a phase III trial with 2,300 lung cancer patients who have had their tumours surgically removed but received little or no other therapy. Other promising vaccine trials include those for WT1 for leukemia (GSK) and Onyvax-P for prostate [7].

The most promising avenue of cancer vaccine research is aimed at better understanding the basic biology underlying how immune system cells and cancer cells interact. Researchers are trying to identify the mechanisms by which cancer cells evade or suppress anticancer immune responses. For example research has shown that some cancer cells produce chemical signals that attract white blood cells known as regulatory T cells, or Tregs, to a tumour site. Tregs produce cytokines that can either stimulate or suppress the activity of killer T cells. When Tregs move close to a tumour, they often release cytokines that suppress the activity of nearby killer T cells. The combination of a cancer treatment vaccine with a drug that would block the negative effects of one or more of these suppressive cytokines on killer T cells might improve the vaccine's effectiveness in generating potent killer T cell antitumour responses [8].

## REFERENCES

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