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# Training the Defense System for Modern-Day Warfare: The Horizons for Immunotherapy and Vaccines for Cancer

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## Opening Remarks

Our defense system also known as the immune system is built to fight the invaders both from inside as well as from outside. With the advent of industrialization of our food system and with the constantly evolving environment where we live, the immune system is challenged with ever increasing permutation and combinations of both outside and inside invaders. Our opinion is that any kind of diseases are related to immunodeficiency to fight it by the host defense system. Cancer is among the most challenging inside invaders that our immune system encounters. Since the immune system is naturally built to protect the host integrity and fight different diseases including cancer, it would be worthwhile and attractive avenue to find the cure for this deadly disease. Immunotherapy is based on the fact that immune system can help fighting against potentially all types of cancer. People with weakened immune systems are more likely to get certain cancers than others. However in some instances, people with even normal immune systems still develop cancer may be because the immune system doesn't see the cancer cells as foreign invaders or the cancer cells (and their antigens) are not different enough from those of normal cells. Sometimes the immune system recognizes the cancer cells, but the response may not be strong enough to destroy the cancer. Besides, cancer cells themselves shed-off substances that keep the immune system in check. To overcome this, researchers have designed ways to help the immune system recognize cancer cells and strengthen its response so that it can destroy the cancer. These backgrounds prompted the emergence of Immunotherapy. Immunotherapy (also called biological therapy or biotherapy) uses the body's own immune system to fight cancer and to reduce treatment-related side effects. It is used to halt or suppress the processes that allow cancer growth, help the immune system identify cancer cells and promote the body's natural ability to repair or replace cells that have been damaged by cancer treatments. Immunotherapy has become an integral part of modern treatment options in oncology, as it is not associated with many of the drawbacks of conventional therapies. Cancer immunotherapy attempts to stimulate the immune system to reject and destroy tumors, and the complexity of the regulation of the immune system gives rise to many different treatment approaches. Both chemotherapy and the tumor itself are known to potentially inhibit immune response. Cancer cells create an immunosuppressive



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microenvironment within the tumor that allows for escape from immune surveillance. Immunosuppressive tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells reside in tumors, and their products along with tumor derived products, create a microenvironment that counters immune activation and attack [1].

## Retrospectives

Utilizing a combination of anti-cancer therapies is often necessary, despite the potency of cytotoxic anticancer agents and specificity of immunotherapy, because neither by itself is often sufficient to eradicate the disease. T-cell enhancement refers to the induction or enhancement of T-cell responses against tumor-associated antigens is particularly important in tumor vaccination strategies. Strategies to stimulate the dormant immune system against tumors are varied and warrant further investigation of their applications to cancer therapy in the future [2].

*Adoptive T-cell transfer (ACT)* using autologous tumor-infiltrating lymphocytes has emerged as an effective treatment for patients with metastatic melanoma [3]. Immunotherapy is widely considered as the fourth treatment modality for patients with cancer, and uses the constantly increasing knowledge in molecular biology, cell biology and immunology. Biotherapy uses naturally occurring biological molecules (e.g., cytokines and antibodies) that works by manipulation of normal biological mechanisms (controlling or inhibiting tumor growth). Important achievements in anticancer drug development are immunotherapeutic strategies recently approved by the US FDA as well as clinical data of the cancer patients treated through clinical trials [4]. This utilizes dendritic cells harvested from a patient to activate a cytotoxic response towards an antigen. These cells are then either pulsed with an antigen or transfected with a viral vector. The activated dendritic cells are then placed back into the patient; these cells then present the antigens to effector lymphocytes. This initiates a cytotoxic response to these antigens bearing cells. T cells with a naturally occurring reactivity to patient's cancer can be found infiltrated in the patient's own tumors. The tumor is harvested, and these tumor-infiltrating lymphocytes (TIL) are expanded *in vitro* using high concentrations of interluekin-2 (IL-2), anti-CD3 and allo-reactive feeders. These T cells are then transferred back into the patient along with exogenous administration of IL-2 and GM-CSF to increase immune cell availability in the tumor vicinity, and thus improve both antigen presentation and T-cell activation and proliferation. Cytotoxic T lymphocyte antigen 4-blocking monoclonal antibodies enhance immune activity by prolonging T-cell activation. Despite the evidence that immune effectors can play a significant role in controlling tumor growth under natural conditions or in response to therapeutic manipulation, it is unclear why malignant cells evade immune surveillance in most cases [5]. The field of immunotherapy is broadly composed of (a) Alternative Medicines-Chinese herbs, dietary supplements and homeopathic medicines, (b) Biological-Pharmaceutical grade products developed by biotechnology/drug companies that are clinically tested and require government approval/clearance for marketing. Within the field of biological products there are three main categories of immunotherapies. (i) *Passive Immunotherapy*: these are comprised of antibodies or other immune system components that are made outside the body (i.e. in the laboratory) and administered to patients to provide immunity against a disease, or to help them fight off an infection. It does not stimulate a

patient's immune system to "actively" respond to a disease in the way a vaccine does. This type of therapy also does not rely on the body to attack the disease rather these immunotherapies employ immune system components (such as antibodies) created outside of the body to destroy the cancer cells. (ii) *Active Immunotherapy*: Active immunotherapies stimulate the body's own immune system to fight the tumor. It includes cancer vaccines, cellular therapies, and Adjuvants. Cancer vaccines as well as the cellular therapies are discussed in detail in separate sections. *Adjuvant Immunotherapy*: An adjuvant is substance which when injected together with an antigenic protein or other materials (like a mAb or cancer vaccine) increases or boosts the immune response to that particular antigen or antigenic parts of the vaccine. Examples include: BCG, KLH, IFA, QS21, Detox, DNP, GM-CSF. Adjuvants have their own associated toxicities. Many adjuvants can only be administered once or twice to humans, and can only be administered sub-cutaneous (injected into the skin or muscle), and cannot be infused. (iii) *Combination immunotherapy*: This is a new class of immunotherapy drugs that possesses both active and passive activity. Some immunotherapy may cause side effects. Compared to the side effects of chemotherapy, the side effects of monoclonal antibodies (MAbs) which are given intravenously are usually fairly mild and are often more like an allergic reaction. These occur mostly during very first administration of the drug. Possible side effects include fever, chills, weakness, headache, nausea, vomiting, diarrhea, low blood pressure, rashes etc. These side effects can interfere with one's daily activities. Therefore, to be effective immunotherapy is often provided in conjunction with other treatment modalities, such as surgery, radiation therapy and chemotherapy. *Limitations of Current Immunotherapy:* Provenge is an autologous cancer vaccine that works by stimulating the patient's own immune system to target prostate cancer cells. It represents an important clinical success and has shown very positive results, however, it is very hard to produce in large quantities. It is an autologous vaccine, meaning one patient - one vaccine (prepared from the patient's own cancer cells). The targets can differ among different patients, and the targets can change when cancer cells mutate. The second major limitation of immunotherapies is that they are often administered late in the cancer therapy cycle, when the patient's immune system is already weakened. In order to achieve a meaningful immunotherapeutic effect immunotherapy should be early in the treatment process. It should be used before any potential adverse effect on the immune system that might have been caused by radiation, chemotherapy and surgery, and before the cancer has possibly become "tolerated" by the affected individual's immune system. Future advances in cancer therapy will require an integrative immunological approach on the finer details of the immune signaling networks that will be directly applicable for designing novel anticancer strategies. Inflammation plays a dominant role at all stages of tumor development: initiation, progression, and metastasis [6]. Tumor-associated inflammation causes a decline in immune function that overrides tumor immunosurveillance and immunotherapy [7]. Understanding the immune regulatory mechanisms of inflammation and balancing them in favor of tumor immunity will help to improve cancer immunotherapy approaches. The success of an immune effector response depends on a fine productive balance between the innate and adaptive components of immunity. Besides providing an effector response, cognate adaptive immune cells are necessary to mediate tissue specificity in the chemokine promoted recruitment of innate immune cells to the site of cancer or other lesions following a pathological insult and generate their effector responses in a controlled

fashion. Identification of the underlying signaling mechanisms responsible for the cross-talk between innate-immune cells and the various populations of effector, and regulatory T cells, as well as B cells, will help decipher new networks of immune regulation. This will reveal new intervention targets applicable for cancer therapy and prevention [8-10]. Immunotherapy represents a new and powerful weapon in the arsenal of anticancer treatments. It seems to offer great promise as a new dimension in cancer treatment. Immunotherapies involving certain cytokines and antibodies have now become part of standard cancer treatment. Although many clinical trials of new forms of immunotherapy are in progress, an enormous amount of research remains to be done before the findings can be widely applied.

## Cancer Vaccines

The central idea behind cancer vaccine is generally meant to boost the immune system to fight against cancer just like normal vaccine does against infection. Developing a vaccine against cancer is fascinating as well as promising area of research. cancer vaccines are in clinical trials. Some research suggests promise in the therapeutic potential of a prototypic melanoma vaccine based on recombinant adenovirus expressing human tumor-antigen, however the magnitude of T-cell immunity evoked by the vaccine was significantly reduced. Success of any cancer vaccine relies on the induction of an effective tumor-specific immune response to break tolerance and to elicit long lasting anti-tumor immunity. Preventative vaccines, like those that protect against viruses or the flu, are given before a person becomes sick. In recent years, scientists have attempted to develop therapeutic vaccines, with the first successful prostate cancer vaccine called Provenge approved in 2010 by the US FDA [11]. In contrast to preventive vaccines the therapeutic cancer vaccines are given to a person who already has the disease. Therapeutic cancer vaccines are designed to treat cancer by boosting the immune system to fight against the cancer. These are active immunotherapies because they trigger patient's immune system to respond. Cancer vaccines are targeted because they do not just boost the immune system in general, they also cause the immune system to attack the cancer cells, honing in on one or more specific tumor antigens. Cancer vaccines typically consist of a source of cancer-associated material (antigen), along with other components, to further stimulate the immune response against the antigen. The challenge has been to find better antigens, as well as to package the antigen in such a way as to enhance the patient's immune system to fight cancer cells that have the antigen. Examples of Cancer vaccines include: Tumor cell vaccines, Antigen vaccines, Dendritic cell vaccines (Provenge), Anti-idiotype vaccines, DNA vaccines, and vector-based vaccines. A cancer vaccine may contain cancer cells, parts of cells, or purified tumor-specific antigens and is designed to increase the targeted immune response against cancer cells already present in the patient. A cancer vaccine may be combined with other substances or cells called adjuvants that help boost the immune response even further. Appropriate activation of dendritic cells (DC) is essential for successful active vaccination and induction of cell-mediated immunity [12]. Antigen presenting cells (APC) are key players in the initiation of an effective immune response [9]. Dendritic cells (DC), which reside in peripheral tissues, are professional APC [12]. Although chemotherapeutic agents at high systemic levels are invariably lethal to immune effector cells, they can actually activate DC when applied locally and might thus act as an

adjuvant in vaccination settings [13]. A similar observation was made by during combined DC vaccination with paclitaxel treatment, resulting in increased anti-tumor responses [14]. Cancer vaccines generally fall into two categories: a) cell-based cancer vaccines, which are created using patient's own cancer-cells that have been presented to and cultured with the patient's own immune system cells. These activated immune cells from the patient are delivered back to the same patient with other proteins (e.g., IL-2) to further facilitate immune activation of these tumor antigen-primed immune cells; and b) vector-based cancer vaccines in which an engineered virus, or other vector, is used to introduce cancer specific proteins and other molecules to the patient in order to stimulate the patient's immune system to recognize the tumor cells and fight the cancer. Both approaches are designed to stimulate patient's own immune system to attack tumor cells. *Limitations of Cancer Vaccines*: Today, most cancer vaccines are targeted. The limitations of targeted vaccines are very similar to the limitations of other targeted therapies like mAbs. Tumor cells mutate as a result of chemotherapy and radiation treatment, and therefore the target antigens on the tumor cells at which the therapy is aimed, also changes. Since the target changes, so the vaccines, which target those specific antigens, become ineffective. Autologous vaccine therapy which are derived from the patient's own tumor and are customized for the same patient present many manufacturing challenges. Autologous therapies are very costly. Many cancer vaccines are poorly immunogenic and require the use of adjuvant to elicit an effective immune response. Though addition of adjuvants may increase immunogenicity of the vaccine, but may also cause increased toxicity. The increased antigenicity of the patient's own cellular derived materials used to produce autologous cancer vaccines may cause auto-reactivity and the subsequent development of autoimmune diseases. Patients treated with genetically engineered vaccines may produce neutralizing antibodies, which could cause subsequent therapies with the same product to become ineffective. Antigen selection and the identification of new target antigens are of high importance in the field of vaccination strategies. Active vaccination with Tumor Associated antigen (TAA) peptides or passive vaccination with specific lymphocytes against these TAAs however did not demonstrate encouraging results in clinical trials. It should be possible to induce an innate immune response which can be tailored to a tumor specific adaptive immune response. Attempts are made at cytokine therapy to circumvent challenges of high systemic toxicity and a lack of specific lymphocyte activation [15].

## Cytokine Therapy

Though immune system is complex involving many cytokines and different kinds of immune cells, however it can be modulated to fight cancer by single or a few cytokines administration using recombinant cytokines or by using the genes that encode for these cytokines. For example Interleukin-2 has been shown complete remission from brain tumor in rodent models [16]. For the therapeutic effect it is very important to use appropriate concentration of these cytokines. Our research has shown that a change in IL-2 concentration can have totally opposite effects on cancer cells [17,18], where rather than inducing apoptosis it may promote cancer growth and metastasis. Several factors should be considered before embarking on cytokine therapy which include; (a) Concentration as discussed above, (b) In-vivo stability of the cytokines in blood tissue, (c) toxicity associated

with recombinant cytokines, (d) bio-availability of appropriate cytokine concentrations in the vicinity of the target cells, and (e) complications associated with cell/viral mediated gene transfer for the cytokine/s. Some preclinical studies showed that cytokines that facilitate type 1 helper T (Th1) cells-mediated immune reactions but not Th2 cells-mediated reactions, when produced in tumors, were effective for anti-tumor responses. Overall cytokine therapy trials have contributed to our understanding of cancer treatment through shedding the light on how to train immune system for tumor-specific immunity.

## Challenges and Future Directions

Though human immune system is very complex that involve ever increasing numbers of cytokines and different cells, but since it has protected the integrity of human body since its evolution, so it has all the necessary power and mechanism to protect from all kinds of diseases including cancer. Future research should be directed towards understanding these abilities and potentials. For example different idiotypic vaccines has been found useful against different specific cancers [19], it would be worthwhile to generate homology model from different antigens and develop universal vaccine that could be useful against wide variety of cancers. Since most of the research has been done in rodent model, future research should also be directed to find out the success rate in human. It would be worthwhile to find if similar strategies could be used in other diseases such as diabetes, and cardiovascular complications. Moreover, using a combination of vaccine and cytokine therapies could be a good choice and the clinical trial for such an approach should be encouraged.

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